FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ADVISORY COMMITTEE FOR REPRODUCTIVE HEALTH DRUGS

THURSDAY, AUGUST 13, 2009

8:00 a.m. to 5:00 p.m.

Hilton Washington, D.C./Gaithersburg

620 Perry Parkway

Gaithersburg, Maryland

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I N D E X

P R O C E E D I N G S

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DR. CARSON: This is the meeting of the FDA's Advisory Committee for Reproductive Health Drugs. My name is Sandy Carson. I'm a professor at Brown University and chair of this committee.

I would like to begin by first thanking the committee members. This is a time of lots of vacations, difficult air travel, and you have really been gracious enough to accept our invitation and done, I'm sure, your preparation. And we thank you very much for being here. I would like the committee to introduce themselves and let's begin with FDA staff.

DR. PAZDUR: Richard Pazdur, Office of Oncology Drug Products.

MS. BEITZ: Julie Beitz, Office of Drug Evaluation three.

DR. BENSON: George Benson, Deputy Director of the Division of Reproductive and Urologic Products.

MS. DEMKO: Suzanne Demko, Medical Reviewer Division of Biologic Oncology Products.

DR. KEHOE: Theresa Kehoe, Clinical Team Leader of Division of Reproductive and Urologic Products.

DR. COLLINS: I'm Michael Collins. I'm at the National Institutes of Health.

DR. ROSEN: Cliff Rosen, I'm an endocrinologist at Maine Medical Center Research Institute.

DR. UZEL: Gulbu Uzel, immunologist and a pediatric rheumatologist at The National Institutes of Health.

DR. BENNETT: John Bennett from NIAID-NIH Bethesda.

DR. EMERSON: Scott Emerson a biostatistician from The University of Washington in Seattle.

MS. BHATT: I'm Kalyani Bhatt; I'm the Designated Federal Official.

DR. JOHNSON: Julia Johnson, chair of OB-GYN University of Massachusetts.

MR. GOOZNER: Merrill Goozner, I'm an independent writer and consultant for consumer groups

on health care related issues.

DR. NELSON: Larry Nelson, reproductive endocrinologist, intramural research program NIH.

DR. MARGOLIS: David Margolis, I'm in the Department of Dermatology and the Department of Biostatistics and Epidemiology at the University of Pennsylvania.

DR. BUZDAR: Aman Buzdar, from the University of Texas, MD Anderson Cancer Center. I'm the medical oncologist with interest in breast cancer.

DR. MORTIMER: Joanne Mortimer, I'm a medical oncologist with an interest in breast cancer, City of Hope.

DR. RICHARDSON: Ron Richardson, medical oncologist Mayo Clinic, Rochester, Minnesota.

DR. GULLEY: James Gulley, medical oncologist with an interest in prostate cancer at the National Cancer Institute.

MS. SOLONCHE: Martha Solonche, patient representative from New York City.

DR. GUT: Robert Gut, Executive Medical Director at Novo Nordisk, I'm an industry

representative.

DR. CARSON: Thank you. And also our transcriber today is Robin Boggess.

There are a few things that we must read into the record. For topics such as those being discussed at today's meeting, there are often a variety of opinions, some of which are quite strongly held. Our goal is that today's meeting will be a fair and open forum for discussion of these issues and that individuals can express their views without interruption. Thus, as a gentle reminder, individuals will be allowed to speak into the record only if recognized by the chair. We look forward to a productive meeting.

In the spirit of the Federal Advisory Committee Act and the Government in the Sunshine Act, we ask that advisory committee members take care that their conversations about the topic at hand take place in the open forum of the meeting.

We are aware that members of the media are anxious to speak with the FDA about these proceedings. However, FDA will refrain from discussing the details

of this meeting with the media until its conclusion. Also, the committee is reminded to please refrain from discussing the meeting topic during breaks or during lunch. Thank you.

Then, also, I would like to remind everybody to silence your cell phone if you have not already done so, and I would like to identify the FDA press contact who is Pat El-Hinnawy.

There you are. Thank you.

Let me ask Kalyani to read the conflict of interest statement.

MS. BHATT: Good morning. The Food and Drug Administration, FDA, is convening today the meeting of the Advisory Committee for Reproductive Health Drugs of the Center for Drug Evaluation and Research under the authority of the Federal Advisory Committee Act of 1972.

With the exception of the industry representatives, all members and temporary voting members of the committee are special government employees, SGEs, or regular federal employees from other agencies and are subject to federal conflict of

interest laws and regulations.

The following information on the status of this committee's compliance with federal ethics and conflict of interest laws covered by, but not limited to, those found at 18 USC Section 208 and Section 712 of the Federal Food, Drug and Cosmetic Act, FD&C Act, is being provided to participants in today's meeting and to the public.

FDA has determined that members and temporary voting members of this committee are in compliance with federal ethics and conflict of interest laws. Under 18 USC Section 208-B3, Congress has authorized FDA to grant waivers to special government employees who have potential financial conflicts when it is determined that the agency's need for a particular individual's service outweighs his or her potential financial conflict of interest.

Under Section 208, Congress has authorized FDA to grant waivers to regular government employees who have potential financial conflicts when it is determined that the financial interest is not so substantial to be likely to affect the integrity of

the individual's service to the government.

Under section 712 of the FD&C Act, Congress has authorized FDA to grant waivers to special and regular government employees with potential financial conflicts when necessary to afford the committee essential expertise.

Related to the discussion of today's meetings, members and temporary voting members of the committee who are special and regular government employees have been screened for potential financial conflicts of interest of their own, as well as those imputed to them, including those of their spouses or minor children and for purposes of 18 USC Section 208, their employers. These interests may include investments, consulting, expert witness testimony, contract grants, CRADAs, teaching, speaking, writing, patents and royalties, and primary employment.

For today's agenda the committee will discuss and make recommendations regarding the new biologic license application for Prolia for the proposed indications of the treatment and prevention of osteoporosis in postmenopausal women and the

treatment and prevention of bone loss in patients undergoing hormone ablation for prostate or breast cancer. This is a particular matter involving specific parties.

Based on the agenda and all financial interests recorded by the members and temporary voting members of the committee, it has been determined that interest in firms regulated by the Center for Drug Evaluation and Research present no potential for a conflict of interest.

To ensure transparency, we encourage all standing committee members and temporary voting members to disclose any public statements that they have made concerning the product at issue.

With respect to FDA's invited industry representatives, we would like to disclose that Dr. Robert Gut is participating in this meeting as a non-voting industry representative acting on behalf of regulated industry. Dr. Gut's role at this meeting is to represent industry in general and not any particular company. Dr. Gut is employed by Nova Nordisk.

We would like to remind members and temporary voting members of the committee that if the discussions involve any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement and their exclusion will be noted for the record. FDA encourages all participants to advise the committee of any financial relationships that they may have with any firm at issue. Thank you.

DR. CARSON: And then Mr. Merrill Goozner, who is our acting consumer representative, has a statement.

MR. GOOZNER: Thank you Dr. Carson.

While I do not have a conflict of interest, I would like to include a statement for the record. When I agreed to become a temporary member of this committee about two months ago, I did not know which company was involved. But when I opened the review material sent to me by the FDA less than two weeks ago, I learned that the company involved was Amgen.

I immediately informed the advisory

committee staff that I have written extensively about Amgen in the past decade in a book and on my own website, much of which could be considered critical. None of those writings involve this drug or this disease.

I told the FDA that some might perceive this as evidence of intellectual bias, but I thought I could provide objective advice representing consumers on this issue. The FDA took the matter under review and informed me yesterday that I could participate in the meeting.

DR. CARSON: Thank you.

Dr. George Benson will now introduce the issues that we are going to discuss today. Dr. Benson is the Deputy Director of the Division of Reproductive and Urologic Drugs.

DR. BENSON: We would also like to welcome you to this morning's advisory committee meeting for denosumab, and we particularly thank Dr. Carson and the members for agreeing to serve on this advisory committee.

This is the original biologic licensing

application for denosumab. Denosumab is a fully human IgG2 monoclonal antibody against receptor activator of nuclear factor kappa B or RANK ligand. RANK ligand stimulates its receptor, RANK, initiating intracellular signalling cascades, which promote osteoclast formation, differentiation, and activation, which leads to enhanced bone resorption and bone loss.

In the immune system, RANK ligand is involved in B cell and T cell differentiation, as well as maturation of antigen presenting or dendritic cells. Denosumab is dosed 60 milligrams every six months as a subcutaneous injection administered by a health care provider.

The new biologic licensing application seeks four separate indications for denosumab. These are treatment of postmenopausal osteoporosis, prevention of postmenopausal osteoporosis, treatment and prevention of bone loss in patients undergoing hormone ablation therapy for breast cancer, and therapy and prevention of bone loss in patients undergoing hormone ablation for prostate cancer.

The primary trial submitted to support

approval of the treatment of postmenopausal osteoporosis indication is an 8,000 patient fracture trial. The other three indications are supported by smaller studies, which use bone mineral density as the primary endpoint. Once an agent has demonstrated fracture reduction in one patient population, the division currently allows BMD to be used as the primary endpoint in studies of other patient populations.

The first two indications, treatment and prevention of postmenopausal osteoporosis, are being primarily reviewed by the Division of Reproductive and Urologic Products, and the two indications dealing with hormone ablation in cancer populations are being primarily reviewed by the Division of Biologic Oncology Products. Denosumab represents the first biologic product and the first monoclonal antibody to seek approval for any of these four indications.

Therapy seeking and indication for treatment of osteoporosis are required to demonstrate fracture efficacy. As previously stated, once fracture efficacy is established for a particular agent, BMD

can be used for evaluation of prevention of osteoporosis and for evaluation of efficacy in other populations or with new dosing regimens.

For comparative efficacy labeling claims between different agents, a head-to-head fracture trial is currently required. BMD findings alone cannot be extrapolated to predict differences in fracture efficacy.

Osteoporosis is defined as a systemic skeletal disorder of compromised bone strength, predisposing an individual to an increased risk of fracture. Currently, an estimated 10 million people in the United States have osteoporosis, 8 million women and 2 million men. An estimated 34 million people have low bone mass and are at risk for developing osteoporosis.

Currently there are 10 products available for the treatment of postmenopausal osteoporosis, five bisphosphonates, one SERM, one parathyroid hormone analog, and three calcitonin products. The majority of these agents also have the prevention of osteoporosis as an indication. These agents are dosed

daily to once yearly.

Prostate cancer is the most commonly diagnosed cancer in men and breast cancer is the most commonly diagnosed cancer in women. Reduction in sex steroid levels is a well recognized etiology of bone loss. No therapies are currently approved to treat bone loss associated with hormone ablation therapy.

Therapeutic monoclonal antibody products have been approved for various conditions, including cancers, organ rejection, and autoimmune disorders. Many have had serious safety issues identified both pre- and post-approval. Some have required medication guides, FDA alerts, or risk evaluation and mitigation strategies. A summary of the safety issues occurring with monoclonal antibodies can be found in Appendix A of the FDA briefing document.

The Food and Drug Administration Amendments Act of 2007 provides new authority to the FDA to require REMS. A REMS is a risk management plan that utilizes strategies that go beyond professional labeling to ensure the drug benefits outweigh risks. A REMS can include a medication guide for patients, a

communication plan for health care professionals, and elements to assure safe use.

The elements to ensure safe use is the most restrictive element that may be required as part of a REMS. These elements can include prescriber training or certification; drug administration limited to certain health care settings; or required monitoring of patients.

Review of the efficacy data shows that denosumab is effective in all four trials, which were submitted to support approval of all four indications. No head-to-head fracture studies, however, comparing denosumab with other agents have been performed.

The primary issues for consideration at today's advisory committee meeting involves safety issues, which have been identified during the review and include the occurrence of serious infections, development of new malignancies, dermatologic adverse events, and findings that suggest a potential for over suppression of bone remodeling.

With regard specifically to the two indications involving breast and prostate cancer

populations, there are further issues for consideration. A growing body of evidence suggests the promotion of tumor growth may exist for therapies in which there is no known direct relationship between the affected receptors and tumor proliferation.

Secondly, the impact of agents for supportive care of cancer patients should be carefully evaluated to identify any detrimental effects on cancer outcomes, such as progression free survival and overall survival.

We will ask the committee this afternoon to consider these safety concerns in the evaluation of the risk/benefit ratio for each of the four bone indications being sought for denosumab. Thank you.

DR. CARSON: Thank you very much. Let me now ask the sponsor to begin their presentation, and Dr. Paul Eisenberg is the senior vice-president and will direct his team through their presentation.

DR. EISENBERG: Good morning. Thank you Dr. Carson, members of the committee. My name is Paul Eisenberg. I'm responsible for Amgen's global regulatory and safety organizations.

First, on behalf of the many Amgen scientists who've worked to develop denosumab over the past 15 years into a therapy to prevent bone loss, we want to thank the committee today for your time and considering the data we will present. It's an extensive presentation this morning and we appreciate that it will take some time.

The clinical realization of the potential of denosumab as a specific inhibitor of RANK ligand as a therapeutic modality is a true example of bench-to-bedside research that translated the discovery of a key mechanism for regulating bone resorption into a novel therapeutic.

I'll be making some additional comments in regard to the specific clinical indications that FDA has highlighted that we're seeking. Following my introduction, Dr. Ethel Siris, who is an expert in osteoporosis, will speak briefly on clinical aspects relating to postmenopausal osteoporosis and bone loss that occurs in women and men treating with hormone ablative therapies, as well as the need for additional therapies.

Following Dr. Siris' presentation, Dr. David Lacey, the pathologist whose lab led the discovery of the RANK ligand pathway, will be commenting on the scientific basis supporting the use of denosumab clinically in the treatment and prevention of bone loss. He is also going to specifically review data that address concerns regarding the RANK pathway in immune responses and the malignancy.

These data are very informative with respect to the clinical context in terms of the data that we'll be presenting from our pivotal registration studies, which Dr. Stehman-Breen will present.

Finally, I'm going to conclude with Amgen's presentation of the ongoing clinical trials and planned studies that continue to support the safety profile of denosumab in these indications. In aggregate, the program we will be presenting this morning presents compelling evidence of efficacy supported by a comprehensive pharmacovigilance program.

Now as noted already, denosumab is a human monoclonal antibody that inhibits RANK ligand. By

inhibiting RANK ligand, it's binding to its receptor on the osteoclast, bone resorption is reduced. Dr. Lacey will be reviewing in greater detail the work of Amgen scientists in understanding this pathway.

As FDA has noted, denosumab has been studied in the treatment and prevention of postmenopausal osteoporosis and in bone loss that occurs in women and men treated with hormone ablative therapies that decrease sex hormone levels. The studies to support the use of denosumab in these indications were developed in collaboration with FDA based on draft guidance on the development of new therapies for the treatment of postmenopausal osteoporosis.

As already highlighted, the regulatory guideline highlights the need to validate that increases in bone mineral density attributable to a new therapeutic translate into fracture reduction as confirmation of increased bone strength induced by that therapeutic.

Amgen's pivotal registration study, the 216 study, and we've provided you handout of each of the pivotal studies that we performed, included both the

fracture endpoint and the BMD assessment. For the prevention of postmenopausal osteoporosis and in the treatment and prevention of bone loss in women undergoing hormone ablation therapy, the BMD was the only endpoint in the studies that we performed, based on the validation of fracture reduction in the 216 study. But in men with prostate cancer treated with ADT, Amgen pursued a more extensive program that included both bone mineral density assessment, as well as a prespecified fracture prevention endpoint.

The rationale for use of denosumab in the prevention of bone loss associated with hormone ablation therapies was the recognition that osteoporotic fractures in these patients have been associated with poor outcomes independent of the success of treatment of the underlying malignancy.

I'll now ask Dr. Siris to comment briefly on the clinical context for the conditions we will be discussing this morning. Thank you.

DR. SIRIS: Thank you very much, and good morning ladies and gentleman. My name is Ethel Siris. I'm an osteoporosis specialist at the Columbia

University Medical Center, New York Presbyterian Hospital in New York City, and I'm the immediate past president of the National Osteoporosis Foundation. I'd like to state for the record that my comments this morning are coming from me and I'm not representing any of those organizations in what I have to say to you today.

Let me start by coming back to what Dr. Benson said a few minutes ago. Osteoporosis is defined as a skeletal disorder that is compromised by reduced bone strength, which predisposes individuals to an increased risk of fracture. Fracture is the complication of having this reduced bone strength. And bone strength is really a function in part of the amount of bone, the quantity, which is something we can estimate when we do a bone density test.

But the reduced bone strength is also a function of the quality of bone. And with bone loss, there is a change in bone microarchitecture such that bone is less well put together and therefore becomes weaker. And you can appreciate this interconnected set of cylinders and plates in normal and here you

have these attenuated struts, this one's broken and this one is in the process of separating, and that causes a loss of bone strength.

Now the United States Surgeon General's report in 2004 highlighted that this is a serious public health problem. Indeed there are, as you heard, 10 million Americans with osteoporosis, another 34 million with low bone mass, which is a precursor to osteoporosis, but more importantly is a risk factor itself. Some people with low bone mass are actually at significant risk.

One in two women over the age of 50 will have a fracture in their remaining lifetimes. There indeed were 2 million fractures in the year 2005, of which 29 percent occurred in men, the remainder in women.

Fractures are associated with significantly negative impacts on the quality of life, and in case of hip fracture, and to some degree vertebral fracture; there is an increase in mortality in the post-fracture period. As you see from the pie chart, about 27 percent of fractures are spine fractures,

14 percent occur at the hip, 19 percent at the wrist, about 7 percent are pelvic fractures, and another third of fractures are at a variety of other skeletal sites. Once you've had one fracture you're at high-risk of more.

There are subsets of individuals who are at a different level of risk and those are individuals who are receiving hormone ablation therapy. Hormone ablation therapy for both breast and prostate cancer is a mainstay therapy for estrogen receptive positive breast cancer and for men with prostate cancer. And indeed, we believe that the number of patients with nonmetastatic cancers undergoing hormone ablation in the United States today includes between 300,000 and 450,000 women with breast cancer who receive aromatase inhibitors and another 140,000 men with prostate cancer undergoing androgen deprivation therapy. These therapies are helping these people to live longer and function better and they are important treatments for them.

Unfortunately, one of the consequences of hormone ablation is bone loss, and this bone loss is

associated with an increased risk for fracture, and depending on which study you look at, its anywhere from an 11 to a 53 percent relative risk of having fractures; and this is a subpopulation that needs to be helped.

Now today we look at the diagnosis of osteoporosis based on measurement of bone mineral density and we use something called a T-score. A T-score, as you see at the bottom, in a postmenopausal patient, represents the number of standard deviations above or below the mean value of bone density in a reference population of healthy young women.

So it's been stated by the World Health Organization that if you have a T-score that is better than minus 1, you're normal. If you're between minus 1 and minus 2.5, you have low bone mass, sometimes called osteopenia, and if you have a T-score of minus 2.5 or below, that's osteoporosis. And while this is a very useful way of helping us categorize people, and indeed diagnosis is based upon T-scores, it turns out this is not the best way to assess who is at increased risk. You have to go beyond T-score to

determine who is at increased risk for fracture.

Now this slide shows data from a study called the National Osteoporosis Risk Assessment, or NORA, which enrolled 200,000 U.S. women, all postmenopausal between 50 and 99, who did not have a diagnosis of osteoporosis and were not receiving treatment for osteoporosis. And at baseline, as shown on the X axis, their bone mineral density values ranged all the way from plus one down to minus 3.5.

At one year post-baseline, data were collected on fractures in that first post-baseline year, and you can see that the fracture rates were the highest in the people with the lowest bone mineral density measurements. And that's the whole point of doing a bone density.

If you look at the population distribution in NORA, shown under this bell shaped curve, you see that the majority of women range from normal down to osteopenic, and that's because there are more people who have an osteopenic T-score than have an osteoporotic T-score in our country. And if we then looked at the actual number of women who fractured,

shown in the yellow bars, it turns out that 52 percent of the people who fractured had osteopenia and that's simply because, although they may have been at somewhat more moderate risk, there are so many more of them, that if you simply think about treating people with osteoporosis, you will miss a great number of people with osteopenia who actually are having the fractures.

And what this tells you is not that you must treat all people with osteopenia. No, it says you must risk stratify people with osteopenia, because some are at low-risk and some are at high-risk and you don't want to miss the people at high-risk, you want to treat those, so the people at low-risk can be reassured and re-evaluated over time.

The way to do this is with a new tool from the World Health Organization called FRAX. FRAX is a tool that helps you calculate the 10 year absolute probability of hip fracture and a group of fractures called major osteoporotic fractures, spine, hip, forearm, and humerus, by taking into account not only the bone density at the hip, but adding to it a series

of validated clinical risk factors, which have been shown to be effective at better predicting who's at risk for fracture. And it basically allows the clinician to make a treatment decision based on absolute fracture risk. Now it's most useful in the patient with osteopenia.

Here's an example of how you use FRAX in a U.S. woman who is 67 years of age. She has a previous fracture. Her mother also broke a hip; these are two important risk factors. And very significantly, her T-score is minus 2.1. She is osteopenic. But because of her age, 67, and her risk factors that are positive, her 10 year probability of a major fracture is 36 percent and her 10 year probability for a hip fracture is 4.7 percent.

How do we use that information?

Well the National Osteoporosis Foundation guide recommends that postmenopausal women and men over the age of 50 presenting with the following, any one of the following, should be considered for treatment. Anyone who has a hip or a vertebral fracture essentially has osteoporosis and should be

treated. Anyone with a T-score of minus 2.5 or below at the hip or the spine has osteoporosis, and this is someone who would fit into the treatment indication for osteoporosis.

But the third category, or those individuals with low bone mass and, by FRAX, a 10 year probability of fracture, the T-scores between minus 1 and minus 2.5 at the hip or spine, and they either have a 10-year probability of hip fracture of 3 percent or greater, the case I showed you was 4.6 percent, or a 10-year probability of major fractures equal to or greater than 20 percent. The patient I showed you had a risk of 36 percent.

So this is an individual who would fall under the prevention indication, because this is somebody who doesn't have osteoporosis, but who is at high-risk for fracture, and therefore we would recommend the patient be treated. And by the way, clinical judgment is also a big part of these decisions. FRAX helps clinical judgment.

Now, as was noted, we are fortunate to have a series of therapies available for our patients and

we are grateful to have them, but I think it's critical to point out that one size does not fit all in postmenopausal women with low bone mass or osteoporosis.

With the oral bisphosphonates, there may well be GI intolerance. Tolerance is a big part of it. Patients won't take the drug if it upsets their stomachs or if it's contraindicated. Clearly, there are side effects for every one of these therapies. They all have side effects, which in some instances prevent you from using the drug, and in other instances the patient is afraid of the side effects and won't take the drug.

There are different efficacy profiles. Some of these drugs are indicated for the prevention of vertebral fracture, some for vertebral and non-vertebral, some for vertebral and hip, some for all three. They vary, but there are different efficacy profiles.

Finally, there are renal issues with bisphosphonates, and especially IV bisphosphonates; you really have to be very careful using these agents

in people with poor renal function.

Very importantly, we have no approved therapies for bone loss in breast and prostate cancer patients who are on hormone ablation therapy. We see these people in the office, we know that they are losing bone, and we don't have an approved treatment for them.

And finally, I would say that one of the biggest problems in our field today is adherence. It turns out that about half of patients put on an oral agent for osteoporosis are not taking it at the end of one year. We therefore want to have treatments that patients will actually take. A twice yearly injection in a primary care doctor's office may offer a considerable convenience for the patient and also allows the doctor to know whether or not the patient is actually receiving that therapy.

I cannot underscore enough how important it is for us to do a better job getting patients to take the treatments we recommend, because if you don't take it, it turns out it doesn't work and you are therefore subjected to the cost, the potential for side effect

without the benefits, so adherence is a critical issue.

Let me say in conclusion that this is a serious public health problem; it affects a great many people. We are getting better at identifying those who are at risk. We need to have a broad range of options so that we truly can tailor therapy to the patient and I think that we have to do a better job, because this is a costly and serious issue that we really have to change in our country.

Thank you very much for your attention. I will turn the podium over to Dr. Lacey.

DR. LACEY: Good morning. Thank you Dr. Siris.

As Dr. Siris, I think has compellingly reviewed, there is, I think, an important need for another option for the treatment of osteoporosis. And what I want to do in this next section is to briefly review the history of the science at Amgen and the therapeutic that we're presenting today, denosumab, which we feel represents a novel and targeted approach to the regulation of bone loss.

So this is a historic slide. Just looking at this slide takes me back about 15 years ago. Amgen was in the midst of a gene discovery program called the Amgen Genome Program, and in that program, we were trying to determine the function of novel genes with the hope that we would find one that would lead to an important new therapy.

One of the first genes that we've identified that we wanted to determine its function, was a gene called osteoprotegerin. The name wasn't osteoprotegerin at the time, but it quickly was named that after some of our observations.

So the two radiographs that you see on this slide are the results of the first experiment, and the way Amgen determined the function was to make animals that overexpressed different gene products. In this case the gene product was osteoprotegerin. And you can clearly see, and it was an amazing thing for me to see the first time I saw this radiograph, that the bones on the right side are very radiodense compared to the bones on the left, normal shape, radiodense.

Now as an academic pathologist who had

recently come to Amgen with a background in bone cell biology, specifically in osteoclast biology, this was a very exciting finding. And so when you think about it, it could be either an osteoblast defect, or an osteoclast defect, we rapidly determined in histologic sections that it was in fact a deficiency in the number of osteoclast that typified this finding. So what we quickly did was make recombinant OPG and put it in tissue culture systems looking for the capacity to blunt osteoclast formation, and, in fact, that was the mechanism.

Now it's been stated before, osteoprotegerin is a member of the tumor necrosis factor receptor superfamily. Superfamily designations, just for those of you who may not know, is a structural relatedness; in other words, protein structure analyzed by analytical methods and we align things into families. The tumor necrosis factor receptor superfamily has been very adaptable. It has functions outside of immunity including in vasculature, the nervous system, skin adnexal formation, and in the basis of this observation here, in bone metabolism.

So using OPG, which is a secreted decoy receptor based on its sequence, we rapidly determined that it bound to a new family member, RANK ligand, and then that implicated RANK as a cellular receptor.

So how do these things function together in the bone microenvironment?

This is going to be a build slide; you have probably the last slide in your handout. Bone mass is determined by the interplay of osteoblast that make bone, osteoclast that resorb bone. Through a series of many studies conducted by Amgen and others, the osteoblast governs this process and responds to systemic factors, including cytokines, growth factors, and hormones. It releases in this figure here. The green either coffee bean or football shaped figures is RANK ligand. It engages the cellular receptor on the surface of osteoclast and their precursors, and it drives an intricate cellular cascade.

Our pathway, or our route, ended this discovery process via the discovery of osteoprotegerin or OPG. It is a secreted decoy receptor. It's also secreted by the osteoblast. And so the osteoclast can

govern in the bone microenvironment activities that support bone resorption through the production of RANK ligand and activities that dampen that process through the production of OPG.

Now, with the knowledge of the family, now, further studies were performed with RANK and RANK ligand, and animals were constructed by deleting those genes. And the way those genes were deleted, they were absent from the time of conception, and so the findings that were revealed in these experiments reflected an impact not only of what would happen in an adult, but also reflects things that occur during embryogenesis and during fetal development.

So what did we learn from these experiments? What we learned and confirmed is that, in fact, this pathway is seminal in its importance for osteoclast formation, function, and survival. Secondly, in the developing embryo, these factors are required for lymph node formation. And an interesting finding is that in adult females, during gestation, this pathway is essential for the proliferative step that occurs in the breast prior to lactation, and so the functions of

this pathway are varied.

That last finding was one of the underpinnings that we have taken forward and applied to our discovery program around the utility of RANK ligand inhibition in oncology.

Now, reflecting on the fact that there was an impact on lymph node formation in the knockout animals, or the gene ablated animals, and the fact that RANK and RANK ligand molecules are expressed on immune cells, we of course, were interested in potential immune activities of RANK ligand inhibition. And I crossed a broad set of experiments here numbering 27 different studies. We've studied RANK ligand inhibition and the basal immune profile, responses to immune challenges, responses to infectious challenges, and autoimmune inflammation models, and find that there is no evidence for immunosuppression.

Now, there were two reasons why we're interested in oncology. Firstly, we knew that the osteoclast was a key cell involved in the bone destructive process that accompanies the malignant

process of tumors in bone. The second discovery, which was the mammary proliferation and the lactation, was the second reason to be involved in cancer. We performed 13 different studies, and we've looked at the impact of RANK ligand inhibition on skeletal tumor progression, the capacity for tumors to metastasize to bone, and found in those cases that RANK ligand inhibition actually suppresses those processes and leads to increased survival.

In mammary tumorigenesis models exploring the combined effect of carcinogen and hormone treatments, RANK ligand inhibition suppresses that process. Importantly, a RANK ligand inhibition does not impact tumors that lie outside of the skeleton, so subcutaneous tumors there is no effect of RANK ligand inhibition. And probably most importantly, the use of RANK ligand inhibition did not interfere with antitumor therapies, and the ones that we've explored include chemotherapy, targeted therapy, and hormonal therapy.

So with that as a background, what I want to discuss in the next several slides is the approach

that Amgen took to identify a novel therapeutic targeting the RANK of RANK ligand pathways. We wanted to find the optimal RANK ligand inhibitor. And to do that, I think that turning back to the model here, we thought that an optimal RANK ligand inhibitor could be patterned after OPG. OPG is very potent. We also wanted a therapy that was selective. And we would like to have a therapy, if possible, that would afford a favorable pharmacodynamic profile that would lead to infrequent dosing intervals, which would be of benefit, particularly in the area of postmenopausal osteoporosis.

So in factoring all those things together and realizing that this was not going to be a pathway of minimal-to-small molecule interdiction, monoclonal antibodies seem to be the ideal approach to this particular therapeutic opportunity.

So with this as a realization, Amgen scientists then went on a hunt to find the optimal monoclonal antibody. The result of that process is denosumab. It's named denosumab. And what it is, is a human IgG2 monoclonal antibody. This IgG2 antibody

is identical to all the other circulating IgG2 antibodies that circulate in your body with the important difference is its antigen recognition domain recognizes human RANK ligand.

The molecule is very potent, 3 peak molar affinity, which should allow for low doses. It is selective against other family members, against other TNF family members. And importantly, it does not recognize rodent RANK ligand, which has precluded our ability to do carcinogenicity studies, and it has a suitable half-life amenable to infrequent dosing intervals. So based on what we were looking for, denosumab was an ideal therapeutic.

So here's how it works. This is, again, a picture of that cartoon again. Denosumab binds to RANK ligand, prevents its association with osteoclast and their precursors. And as a result, bone resorption is suppressed as a result of an effect on osteoclast pathway.

So preclinically, we've looked at the effects of denosumab in a nonhuman primate model of postmenopausal osteoporosis or hormone ablation, and

this is the OVX primate model. And the results of the experiment were shown in this slide with bone mineral density on the left, bone strength on the right.

I'll just quickly step through the findings. In the OVX animals alone, over a six month period, they dropped their bone mineral density by about 5 percent to 6 percent. Denosumab treated OVX animals increased their bone mass by that same amount. But within three months, that increase with denosumab continues out to 16 months, where there is a difference between baseline of 11 percent and a difference between the OVX and denosumab group and the OVX alone, being approximately 16 percent.

Perhaps the most exciting result on this slide is the bar graph on the right, and that’s looking at the effect of this treatment on bone strength. And what's unusual about this result is the denosumab treated animals not only have strength that's above the OVX control, but also above the sham. So this implication is this increase in bone mass has led to bones that are very strong.

So in summary, denosumab is a potent

selective RANK ligand inhibitor that suppresses osteoclast formation, function, and survival. Denosumab could not be used in the traditional rodent carcinogenicity studies and that’s according to guidelines.

In safety studies, nonhuman primates were exposed to denosumab, but up to 150 fold to human exposure for 12 months. And the only findings that were found were those that you would expect in bone. And lastly, denosumab increased bone mass and strength in ovariectomized nonhuman primates in a 16 month study, the one I just showed you.

So in conclusion we think that denosumab represents an ideal therapy targeted at a key regulator for osteoclast formation activation and survival.

Now I'd like to introduce Catherine Stehman-Breen who will go over the efficacy and safety results from our clinical trials. Thank you.

DR. STEHMAN-BREEN: Good morning. My name is Catherine Stehman-Breen and I'm the bone therapeutic area head at Amgen. Now you've heard from

Dr. Siris about the public health impact of bone loss, both due to age and to hormone ablation therapy and the need for innovative new therapies. You've just heard from Dr. Lacey about the exciting preclinical discoveries 15 years ago that have formed the basis of the denosumab clinical program and the targeted mechanism of action of denosumab that uses the body's own natural mechanisms to regulate bone turnover.

I'm going to spend my portion of the presentation highlighting how these preclinical discoveries have translated into remarkable efficacy and a favorable safety profile. Now the denosumab clinical program is a large program. There were 30 studies included as part of the biologic license application. I'm going to focus my presentation on the four pivotal studies that are highlighted here.

I'll begin my presentation by summarizing the efficacy data from the studies in the treatment and prevention of bone loss. I'll follow that by summarizing the efficacy data from the two studies in the treatment and prevention of bone loss due to hormone ablation therapy. And then I'll conclude my

presentation by summarizing the aggregate safety data from these four studies.

I'm going to start with the clinical efficacy evaluation in the treatment and prevention of postmenopausal osteoporosis. This data will demonstrate significant reductions in bone resorption that translate into robust increases in bone mineral density and importantly reductions in fracture risk.

Now this slide summarizes the study design for our PMO fracture study. This study was conducted to determine whether denosumab administered at 60 milligrams subcutaneously every six months, the same dose that was used in all of our bone loss clinical trials, would reduce the incidence of new vertebral fracture, in addition to two key secondary endpoints, non-vertebral fracture and hip fracture. New vertebral fracture was identified morphometrically by accessing reductions in vertebral height. All of our fractures were confirmed using an external central reader.

The women that were included in this study were required to have osteoporosis with T-scores that

were between negative 2.5 and negative 4 at either the lumbar spine or the total hip. Because this was a placebo controlled study, women were not allowed to enroll if they had any severe or more than two moderate vertebral fractures. It is also important to note that this study didn't exclude women on the basis of renal function. And as Dr. Siris pointed out, this is an area of unmet medical need.

Seventy-eight hundred and eight women were randomized to either receive denosumab or a placebo. They were followed for 36 months, and during that period they received calcium and Vitamin D as all subjects did in our clinical trials.

Now this study had an important component to it and that’s an open-label 2 study. Forty-five hundred and fifty women were enrolled in this long-term extension study, where they will be followed for an additional seven years, and this will provide important long-term safety data in this population.

Now these are the baseline characteristics of the population that we studied; 82 percent of the women in the placebo group and 84 percent in the women

that received denosumab completed the study. The mean age of the women was 72 years, and as you can see, most of the women qualified based on their lumbar spine bone mineral density. The prevalence of vertebral fracture at baseline was 23.4 percent in women receiving placebo and 23.8 in those women receiving denosumab.

Now administration of denosumab resulted in rapid and sustained reductions in bone turnover as reflected here by reductions in serum C-telopeptide, or CTX, which is a collagen breakdown product. Serum levels of CTX over the course of the study are illustrated in yellow and time is on the horizontal axis, while percent change from baseline is on the vertical axis. As you can see, after administration of denosumab, there is a rapid 86 percent reduction in CTX by month 1. Over the remainder of the six month dosing interval, there is a slight attenuation in the reduction of CTX with an 86 percent reduction at the pre-dose time point at month 6.

Now if you will focus on month 6, 12, 24, and 36, these are the pre-dose time points. And as

you can see, the level of reduction in CTX is generally maintained over that period with a 72 percent reduction at the 36 month pre-dosing interval. And it is also interesting to note that 100 percent of subjects had reductions in CTX after the first dose of denosumab.

Now these reductions in bone turnover translated directly into increases in bone mineral density. The difference in the mean lumbar spine bone mineral density was 9.2 percent at 36 months and 6 percent at 36 months at the total hip. These increases in bone mineral density were maintained over the course of the study and, although not shown here, have been maintained over six years in our Phase 2 study.

Now the PMO study successfully met its primary endpoint, demonstrating significant reductions in the incidence of new vertebral fracture. Denosumab reduced the risk of new vertebral fracture at one, two, and three years. At three years, the subject incidence of new vertebral fracture in the placebo group was 7.2 percent and 2.3 percent in the denosumab

group, resulting in a 68 percent reduction in the risk of new vertebral fracture. Risk reduction was consistent over time and was seen as early as one year. It did not vary across a wide variety of patient characteristics, including renal function.

Now this study also met its key secondary endpoint, demonstrating a significant reduction in the risk of hip fracture. As you can see in this figure, there was a 40 percent reduction in the risk of hip fracture at 36 months. This reduction was seen early as you can see by the early separation of the Kaplan-Meier curve.

This study also met its other secondary endpoint, demonstrating reduction in the risk of non-vertebral fracture. As you can see, at 36 months there was a 20 percent reduction in the risk of non-vertebral fracture. As you heard from Dr. Siris, these types of fractures, which include wrist, humerus, hip, and a variety of other osteoporotic related fractures, are an important source of morbidity and mortality in this patient population.

Now I've summarized the key efficacy data

from the study, but this study also had another key component to it, and that was the bone biopsy study. And I'd like to summarize some of the results of that substudy.

Now the primary reason to do a bone biopsy when assessing a new therapeutic is to ensure that the bone histology has not been altered in a negative way by that therapeutic, and this was demonstrated in a comprehensive evaluation of 241 biopsies that were obtained at baseline, 12, 24, and 36 months in three different studies. These biopsies were obtained at the iliac crest.

A bone biopsy from a denosumab treated subject, a representative biopsy that was obtained at 12 and 24 months is illustrated on the left side of the slide. It demonstrates normal lamellar bone with no evidence of any abnormalities that you might be concerned about, such as marrow fibrosis, osteomalacia, or woven bone.

Measurements of bone remodeling using these biopsy specimens, which is termed histomorphometry, demonstrated findings that were also consistent with

reductions in bone turnover. Using one of these assessments that’s called tetracycline labeling, we observed that about a third of the subjects didn't demonstrate any tetracycline labeling in either the cortical or trabecular bone. This is consistent with the mechanism of action of denosumab and also the level of reduction in bone turnover that we observed with the serum marker CTX.

Now we recognize that this level of suppression has generated some concern, but it's important to keep in mind that it's this level of suppression that has also resulted in increased bone strength in our preclinical models, increases in bone mineral density and reductions in fracture risk in our clinical studies. But as you will see when I summarize the safety data, it has also not been associated with any adverse consequences that one might be concerned about with reductions in bone turnover, such as atypical fractures, abnormalities in fracture healing, or osteonecrosis of the jaw.

Now we recognize that this study is a three year study, but as you'll hear later on in the

presentation, we will continue to monitor for this over the long-term.

Now let's turn and highlight the study design from our prevention of osteoporosis study. As Dr. Siris pointed out, there are many women who don't have osteoporosis who are at high-risk of fracture. And as she pointed out, this is due to a wide variety of well characterized risk factors. The PMO prevention study was conducted to determine whether denosumab would result in greater increases in lumbar spine bone mineral density at 24 months.

Women who were enrolled in the study were required to have lumbar spine T-scores that were in the osteopenic range between negative 1 and negative 2.5. Three hundred and thirty-two women were randomized to either receive denosumab or a placebo and were followed for 24 months.

Now this study also had an important safety follow-up study, and that was a 24 month follow-up period that was designed to assess the effects of discontinuation of denosumab on both serum CTX and on bone mineral density. I'm gonna begin by summarizing

the efficacy data and then I'll follow that by describing the off treatment data.

Now this slide describes the baseline characteristics of the population. As you can see, 87 percent of the subjects completed the study in the placebo group and 86 percent in the denosumab. As expected, the mean age was younger than in our PMO fracture study and most of the women qualified for the study based on their lumbar spine bone mineral density.

Now the difference in the mean bone mineral density was 7 percent at the lumbar spine and 4.5 percent at the total hip. As you can see, these increases in bone mineral density were maintained over the course of the study and are quite similar to that that was observed our postmenopausal osteoporosis fracture study.

Now as I said, there was an off-treatment period after the initial 24 months of the study. The reversibility of denosumab is reflected by serum CTX, illustrated here by the yellow line, with time on the horizontal axis and serum CTX values on the vertical

axis. After discontinuation of denosumab, osteoclast function returns, bone turnover markers increased transiently above baseline, and then subsequently decreased back to near baseline levels. It is important to note that this pattern is consistent with other reversible antiresorptives, such as estrogen and raloxifene.

Now these CTX values directly translate into what we observed with regard to bone mineral density. Again, following the discontinuation of denosumab, osteoclast function returns, bone is resorbed, bone mineral density declines, and at 48 months remains 1.8 percent above that observed in the placebo. These data suggest that denosumab treatment arrests the bone loss that would normally have occurred without treatment.

Now I finished summarizing the clinical efficacy data from the treatment and prevention of osteoporosis. These data have demonstrated significant and rapid reductions in bone resorption that have translated into robust increases in bone mineral density, and most importantly have

demonstrated significant reductions in fracture risk at the spine, at the hip, and at the non-vertebral sites.

I'm going to turn now and highlight data from our hormone ablation therapy studies. As you heard from both Dr. Eisenberg and Dr. Siris, there are no approved therapies for this indication, which is due to hormone ablation therapy, critical therapies in these patients. It is important to remember that women with breast cancer that are receiving androgen deprivation therapy have profound estrogen deficiency. It is the result of both their aromatase inhibitors, but also as the result of menopause.

You will see from these studies that denosumab results in increases bone mineral density, and importantly in men with prostate cancer receiving androgen deprivation therapy, reductions in vertebral fracture risk.

The HALT breast cancer study was designed to confirm that women with bone loss that is the result of estrogen deficiency, due to aromatase inhibitors, would have similar bone mineral density increases as

women with bone loss due to estrogen deficiency that is the result of aging. As you can see, the study design is almost identical to our PMO prevention study.

The HALT breast cancer study was conducted to determine whether denosumab would result in greater increases in lumbar spine bone mineral density than placebo at 12 months. Similar to the prevention study, women who enrolled in the study were required to have bone mineral densities that were in what's termed the osteopenic range or between negative 1 and negative 2.5. The women were required to have nonmetastatic disease, and as a reminder, all of these women were postmenopausal. Two hundred and fifty-two women were randomized to either receive denosumab or placebo and followed for 24 months.

The baseline characteristics of this population are highlighted here; 79 percent of the women in the placebo group and 83 percent of the women in the denosumab group completed the study. The mean age of the population is very similar to what was observed in our PMO prevention study. And, again,

most of the women qualified for the study based on their lumbar spine bone mineral density.

This study met its primary endpoint demonstrating significant increases in lumbar spine bone mineral density. The difference in the mean bone mineral density was 7.6 percent at the lumbar spine and 4.7 percent at the total hip. Now these figures may look familiar to you as the increases in bone mineral density are almost identical to that that we saw in our prevention study.

Now the HALT prostate cancer study was conducted to determine whether denosumab would result in greater increases in lumbar spine bone mineral density than placebo at 24 months in men with prostate cancer receiving androgen deprivation therapy. Men enrolled in the study had nonmetastatic prostate cancer and required to be either more than 70 years of age, or if they were less than 70 years of age, they had to have a history of osteoporotic fracture or a T-score of less than negative 1 at the lumbar spine, total hip, or femoral neck; 468 men were randomized to either received denosumab or placebo and were followed

for 36 months.

Seventy-seven percent of the men in the placebo group and 80 percent of the men in the denosumab group completed the initial 24 months of the study. At 24 months, the study was extended for an additional 12 months, and upon consent, as expected, there was some dropout resulting in 61 percent of the subjects in the placebo group and 64 percent of the subjects in the denosumab group completing the study. The mean age was 75 years and the prevalence of vertebral fracture was 23.7 percent in the placebo group and 21.1 percent in the denosumab group.

This study met its primary endpoint, demonstrating significant increases in lumbar spine bone mineral density. The difference in the mean bone mineral density was 7.9 percent at the lumbar spine and 5.7 percent at the total hip. These increases were maintained over the 36 months of the study.

Now importantly, this study also met its key secondary endpoint, demonstrating significant reductions in the incidents of new vertebral fracture. At 36 months, there was a 62 percent reduction in the

incidence of new vertebral fracture.

Now before I turn and begin to describe the safety data, I think it's important to point out the consistency of the data that we've seen across a wide variety of populations.

This study shows the percent change from baseline in either lumbar spine bone mineral density or hip bone mineral density at two years in each of the populations studied, and illustrates the remarkable consistency of bone mineral density gains.

But perhaps more striking is the consistency of fracture risk reduction that's illustrated here, the magnitude of the reduction in fracture risk in women with postmenopausal osteoporosis was 68 percent, and in men with prostate cancer receiving androgen deprivation therapy was 62 percent.

Because the mechanism of action of denosumab is targeted using the body's own natural mechanism to regulate bone turnover, the impact of denosumab on bone is highly consistent across a broad range of populations, including those with renal insufficiency, and is independent of fracture risk.

I've finished highlighting the clinical safety evaluation. These data have demonstrated significant increases in bone mineral density and, importantly, reductions in fracture risk. I'm going to spend the rest of my presentation highlighting the clinical safety evaluation.

This clinical safety evaluation was conducted with more than 13,000 patient years of follow up. I'm going to begin by summarizing overall adverse events and then highlight a number of prespecified adverse events of interest. Overall, adverse events were balanced between those receiving placebo and those receiving denosumab. The incidence of serious adverse events was 24.3 percent in subjects receiving placebo and 25.3 percent in those receiving denosumab. Withdrawals leading to study discontinuation or stopping study drug was unusual and balanced between the two groups.

There were 20 less deaths in those subjects receiving denosumab, and for that reason we decided to conduct a time-to-event analysis that’s illustrated here.

As you can see with denosumab illustrated by the yellow line, the proportion of subjects surviving was greater in those receiving denosumab than placebo. The hazard ratio for death was .76 and although not statistically significant at a p-value of .08 was intriguing.

The overall adverse events in those subjects receiving hormone ablation therapy was similar, 87 percent in those subjects receiving placebo and 87.8 percent in those subjects receiving denosumab. Serious adverse events occurred in 27.6 percent of subjects receiving placebo and 31.6 percent of those subjects receiving denosumab. Again, withdrawals leading to study discontinuation or stopping of study drug were rare and balanced between the two groups. And as you can see, the overall incidence of death was similar between the two groups.

Now in order to better understand the impact of denosumab on disease progression in men with prostate cancer receiving androgen deprivation therapy, we conducted a prespecified analysis in order to assess the incidence of PSA rise, or prostate

specific antigen, which is an important marker of disease progression amongst men that demonstrated castrate levels of testosterone.

In this assessment, PSA was measured centrally in a prespecified schedule, and using the sensitive criteria that are illustrated on this slide, we demonstrated similar levels of PSA rises. In those subjects receiving placebo, PSA rises occurred in 13 percent of subjects and 13.6 percent of subjects receiving denosumab.

In an additional analysis, that’s described in the lower portion of this figure, the proportion of men that had a PSA rise greater than 5 was similar at all time points that PSA was assessed. These data suggest that denosumab does not have an impact on prostate cancer progression.

Now it's also important to look at survival, and we did a similar Kaplan-Meier analysis. And as you can see, the hazard ratio for death in those subjects receiving denosumab was the same as those subjects receiving placebo.

Now as I said, we had a number of adverse

events of interest that were prespecified. I'm going to describe in detail a number of these to you. There are two that have been highlighted in your briefing document that I won't detail, and that includes hypersensitivity where the event rates of adverse events that might be associated with hypersensitivity were balanced between those subjects receiving denosumab and those receiving placebo. I also won't detail the immunogenicity results as the incidence of binding antibodies was very low and there were no subjects that had antibodies that neutralized denosumab.

There were two adverse events that we observed over the course of the studies and I'll complete the safety presentation by highlighting those.

Now let's start with hypocalcemia. It's not unexpected that any drug that decreases bone resorption might result in reductions in serum calcium. Treatment with denosumab was associated with mild-to-moderate and transient decreases in calcium, which were less than 3 percent at month 1, and when we

did a careful assessment at the nadir of calcium at day 10, it was 3.1 percent. Calcium levels less than 8 mg per deciliter were rare and were seen in less than 0.1 percent of subjects. They resolved spontaneously or with supplemental calcium. We observed no subjects with serum calcium levels below 7. Symptomatic hypocalcemia was rare and was balanced between those subjects receiving denosumab and those subjects receiving placebo.

We looked carefully for any evidence of nonunion or delayed fracture healing. And as you can see in this table, these events were uncommon and were balanced between those subjects receiving denosumab and those receiving placebo.

Now we also sought to determine whether denosumab had any clinical impact on the immune system. As illustrated in this slide, the overall adverse events of infection were of similar frequency between those subjects receiving denosumab and those subjects receiving placebo. Serious adverse events of infection occurred in 3.4 percent of subjects receiving placebo and 4.3 percent of subjects

receiving denosumab, a difference that was not statistically significantly different.

Adverse events leading to study discontinuation occurred infrequently and fatal adverse events were similar between the two groups with 12 events in the placebo group and 6 events in the denosumab group.

Although there was no difference in overall adverse events, there were two adverse events that are worth comment. One is infective arthritis and the second is endocarditis. There were eight events that were coded to infective endocarditis in the denosumab group and none in the placebo group. It is important to note that none of these events were hospitalized nor did they receive IV antibiotics. And, therefore, it is unlikely that these were classic events of aseptic joint.

Although there were three cases of endocarditis in the PMO fracture study, there were also two cases of endocarditis in the HALT prostate cancer study demonstrating a similar frequency across the program.

Now in order to better understand the difference in serious adverse events of infection, we assessed the types of serious adverse events of infection that might account for this difference. We first looked at opportunistic infections, as one might hypothesize that a generalized immunosuppressive effect would result in an increase in the incidence of opportunistic infections, and as you can see from the table, opportunistic infections are well balanced between those subjects receiving placebo and those subjects receiving denosumab, suggesting that these data don't demonstrate an overall immunosuppressive effect of denosumab.

In order to assess what accounted for the numerical differences in serious adverse events of infection, we looked at each preferred term. And this slide illustrates the most common serious adverse events of infection.

It is important to note that pneumonia, which is the most common serious adverse event of infection, was well balanced between the two groups. In addition, sepsis, which would be probably the most

worrisome outcome of infection, is also of similar frequency between the two groups.

The majority of the numeric imbalance in the incidence of serious adverse events of infection was accounted for by adverse events of diverticulitis, infections of the urinary tract, and skin infections. We have provided a detailed analysis of the difference in the incidence of diverticulitis and urinary tract infections in your briefing document. Although I won't provide a detailed analysis in this presentation, I'm happy to answer any questions during the Q&A session.

What I'd like to do is focus on the difference in skin infections. Overall, skin infection adverse events were balanced between the two groups. However, there were more hospitalizations for skin infections in subjects receiving denosumab than subjects receiving placebo in women with postmenopausal osteoporosis. This slide illustrates the various types of skin infections that led to hospitalization. As you can see, the majority of these were comprised of cellulitis or erysipelas,

which on review of the case reports appear to be used interchangeably.

Now the majority of these skin infections were of the lower extremity, all but two. Fifty-four percent of the subjects who reported these events in the osteoporosis study had preexisting conditions that might place them at increased risk for lower extremity infections, including vascular disease or venous ulcers or skin wounds.

There was no predominant microbial agent that was identified. The mean hospital stay in those subjects receiving denosumab was four days and none of these subjects discontinued investigational product. There also didn't appear to be a relationship to the duration of treatment or the time since last dose, and it's important to note that there was only one recurrence despite continued therapy with denosumab.

So in summary, overall adverse events of infection were well balanced between the two groups. There was no evidence for an increased risk of opportunistic infections. Skin infections resulting in hospitalizations occurred in greater frequency in

denosumab treated subjects that had postmenopausal osteoporosis. Recurrent infections were infrequent despite continued RANK ligand inhibition, and, importantly, there was no increased risk of sepsis or death observed in those subjects treated with denosumab.

Now because RANK, RANK ligand, and OPG, the access has been speculated to play a role in vascular biology, we paid careful attention to whether or not denosumab might impact cardiovascular risk. All serious adverse events of cardiovascular nature were adjudicated by an external adjudication committee. As you can see from this slide, all cause mortality and cardiovascular death were lower in those subjects that received denosumab. And when one aggregates all cardiovascular events, the frequency and risk was identical between those receiving denosumab and those receiving placebo, suggesting that denosumab does not have an impact on cardiovascular risk.

Now because there has been an association between bisphosphonates and the development of osteonecrosis of the jaw, we paid careful attention

for the development of osteonecrosis. Potential cases were identified in the adverse event database using prespecified search criteria that were based on FDA advisory committee recommendations. Potential cases of osteonecrosis of the jaw were adjudicated by an external adjudication committee. There were no positively adjudicated cases of osteonecrosis jaw in either women with postmenopausal osteoporosis or in those subjects receiving hormone ablation therapy.

I'd like to spend a little bit of time highlighting data from our analysis of malignancy. Now both the FDA and Amgen use what's called the MedDRA coding system, which is the standard system that’s used by the FDA and all pharmaceutical companies. Now the MedDRA coding system uses a hierarchal approach where at the highest level, adverse events are grouped by body location and don't really have a lot of pathophysiologic commonalities between these adverse events. This table uses these high level groupings. And, for example, if you look, for example, at reproductive neoplasms it includes a wide variety of neoplasms from uterine cancer to

ovarian cancer to vulvar cancer.

When you look at these large groupings, you can see that there are numerical differences in the two groups and that would be expected in a randomized trial with some numerical differences favoring denosumab and some favoring placebo as highlighted in yellow.

Now the system isn't really intended to provide a lot of clarity around clinical concepts, but instead is a way of organizing data. You can gain greater clarity by looking at the individual terms where there may be some small imbalances between the two groups.

In order to provide this sort of detail, I'm going to really drill down in five of these high level groupings. I'll begin by covering breast and then reproductive, gastrointestinal, endocrine, and hematologic. But before I begin, it's useful to note that I'm focusing on only those events which occurred at a greater frequency in the denosumab group. There were others that occurred at a greater frequency in the placebo group, such as malignant melanoma and lung

cancer, but these we felt were simply imbalances that were due to chance.

Now let's begin with breast cancer. In the PMO fracture study, we actually had a specific case report form to collect important and detailed information about prognostic factors with regard to breast cancer, because our preclinical data had actually suggested a protective effect of denosumab.

When we looked at this data, we were able to differentiate between those subjects that had new diagnosis of breast cancer versus those that were recurrences and that’s illustrated here. You can see that 26 subjects in the placebo group and 28 subjects in the denosumab group had new diagnosis of breast cancer over the course of the study.

There were two recurrences of breast cancer in the placebo group and six in the denosumab group, but it's important to note, as is highlighted on this slide, that two of these recurrences in the denosumab group occurred during the first month of the study, suggesting that these recurrences were probably preexisting at the time that the subjects enrolled

into the study.

Now it's also been highlighted that there were 20 subjects in the denosumab group and 10 in the placebo group that discontinued the study due to the adverse event of breast cancer. Now there are many reasons that subjects discontinue from clinical trials, but probably the most worrisome would be if there were some phenotypic difference between those breast cancers in the denosumab group and those in the placebo group.

As you can see, some of the important prognostic factors, including stage, node status, and histology are highlighted here and there doesn't appear to be any differences that would suggest poor prognostic factors in the breast cancers in the denosumab group.

Now let's turn and summarize the reproductive neoplasms that are highlighted here. As you can see, this large grouping includes a variety of neoplasms including uterine, ovarian, cervical, and vulvar. Endometrial or uterine cancers were similar in frequency between the two groups. There were five

ovarian neoplasms in the placebo group and 11 in the denosumab group. Two of those endocrine neoplasms in the denosumab group were benign cystadenomas resulting in five in the placebo group and nine in the denosumab group.

Cervical neoplasms occurred in one placebo subject and three subjects in the denosumab group. One of these cervical neoplasms was a carcinoma in situ in the denosumab group, resulting in one cervical cancer in the placebo group and two in the denosumab group.

Now if we look at the gastrointestinal neoplasms, you can see here that, again, they're comprised of a variety of different types of cancer. Colorectal cancers occurred with similar frequency. Pancreatic cancer occurred in three subjects in the placebo group and eight in the denosumab group. Gastric cancer occurred in three subjects in the placebo group, seven in the denosumab group, and esophageal cancer, oral cavity cancers, and a variety of miscellaneous gastrointestinal cancers occurred at the same frequency in the two groups.

With regard to endocrine neoplasms, this was comprised of thyroid neoplasms and carcinoid of the stomach. Thyroid neoplasms occurred in two subjects in the placebo group and six in the denosumab group. Of those neoplasms there were a number that were thyroid nodules, which were benign, two in the placebo group and four in the denosumab group, resulting in invasive thyroid cancers in two subjects in the denosumab group and none in the placebo group.

Now finally it was highlighted that there were three subjects with hemopoietic neoplasms in the denosumab group and none in the placebo group. And it is useful, perhaps, to walk through these three subjects.

The first subject had an adverse event of essential thrombocythemia. Now when we looked at the baseline laboratory values of this subject, you can see that the platelet count was 425,000, suggesting that this subject had preexisting thrombocythemia at study entry.

The second subject had a pseudolymphoma of the right shoulder. This was a polyclonal lymphoid

infiltrate that was in response to a tick bite. The subject was diagnosed with Lyme disease and after doxycycline therapy the event resolved.

Now the last subject had an adverse event of lymphoproliferation of B cells that was deemed by the investigator benign. When we looked at the baseline laboratory values, the white blood cell count was elevated on entry in the study and the last on study white blood cell count was 10.2 with 66 percent lymphocytes.

Now before I move on, I would like to highlight one additional issue. The FDA's briefing document highlighted that there were three subjects in our dose finding study that died of new malignancy. While it's understandable that there was concern regarding these deaths, it's important to keep in mind that this was a four year study with 412 subjects, with a mean age of 64. And there was a sevenfold more women that were randomized to receive denosumab than placebo, therefore it's not unexpected that there were more deaths in the denosumab group than the placebo group. Importantly, the overall incidence of

malignancies was well balanced between subjects in each group.

In summary, in our preclinical studies, RANK ligand inhibition did not promote cancer development or progression and these studies demonstrated that denosumab might have a beneficial effect. There was no statistical difference in the overall incidence of malignancies in the bone loss program. In the PMO fracture study there was no increased risk of death due to neoplasms, and similarly in the HALT prostate cancer study there was no increased risk due to death or due to neoplasms.

Now as I highlighted, there were two adverse events that were observed over the course of the study. The first was eczema adverse events.

Eczema was observed more frequently in the postmenopausal osteoporosis program with an incidence of 1.7 percent in the placebo group and 3.1 percent in the denosumab group. There were only two serious adverse events amongst these, 97 percent of these events were mild-to-moderate in severity. Only six subjects had recurrences despite continued therapy and

the mean duration of the events was 78 days in the denosumab group and 93 days in the placebo group.

The other adverse event that we observed over the course of the study was cataracts. Cataracts were observed more frequently in men with prostate cancer receiving androgen deprivation therapy with an incidence of 4.7 percent in these men treated with denosumab and 1.2 percent in subjects receiving placebo. We didn't observe this in women with postmenopausal osteoporosis.

It's important to note that the incidence of cataracts in the placebo group in the HALT prostate cancer study was actually quite low. It's also useful to point out that these cataracts were not identified by ophthalmologic exam and were just through adverse event reporting. And it appeared that most of these cataracts were actually cataract surgeries. There also is no known biological mechanism that might underlie this imbalance.

The data I've summarized for you from approximately 13,000 patient years of exposure to denosumab has demonstrated that denosumab has a

favorable safety profile. Overall, adverse events were mild-to-moderate in severity and were well balanced between the two groups. The overall incidence of eczema was observed more frequently in women with postmenopausal osteoporosis and cataracts were observed more frequently in men with prostate cancer receiving androgen deprivation therapy. Slightly more women with postmenopausal osteoporosis developed skin infections that required hospitalizations.

We believe that our analysis did not demonstrate an increased risk of malignancy or an overall immunosuppressive effect of the drug. However, we recognize that defining the safety profile is an ongoing process and we have designed a comprehensive program that includes clinical trials and observational studies to further define the safety profile.

So I'm now going to turn the podium back to Dr. Eisenberg who will detail this pharmacovigilance program that demonstrates our commitment to that end.

DR. EISENBERG: Thank you. We've presented

quite a bit of data. The last portion of the presentation is quite important, because as we think about pharmacovigilance, it really ideally should reflect continuous and comprehensive assessment of benefit/risks throughout a development program, as has been the case with denosumab.

As Dr. Lacey described, Amgen continues to use preclinical models as we have in the past to define the biology of RANK ligand inhibition. Work has gone on for about 15 years in this area and will continue to go on to understand the biology better.

The clinical development program Dr. Stehman-Breen described has been large, appropriately so, comprehensive, and included several approaches that we used to enhance detection of safety signals. We prespecified events of interest; we did that to ensure that we capture all potential events that occur in the areas that we discussed.

We had independent cardiovascular and ONJ adjudication committees to adjudicate the events as we've highlighted. And not surprisingly given the size of the program, we've observed small differences

in adverse events between both groups. And in each area of concern, we've looked to understand the clinical course and fully understand the potential safety signals.

In addition, the development program was appropriate for a program in bone loss, it utilizes biomarkers, imaging, and bone biopsy to characterize bone strength and bone quality.

I'm now going to describe a comprehensive pharmacovigilance program that we've planned that includes data from additional controlled clinical trials, long-term follow-up studies, and proactive safety surveillance.

Now the first issues I'd like to address are concerns specific generally to the safety of monoclonal antibodies. Monoclonal antibodies represent an evolution of the use of antibodies to inhibit therapeutic targets, which has evolved over many years. For example in women and children, many of you are familiar with RhoGAM, which is used to prevent Rh immune responses and there's a human monoclonal antibody recently, Synagis, that's noted in

the FDA's briefing documents, which was developed for the treatment of RSV infections in children.

Monoclonal antibodies also, as highlighted, have proved particularly useful in treating very serious diseases, cancer and autoimmune diseases, because they are very highly specific and efficacious in inhibiting their targets. But as I've highlighted here on this slide, a lot of the safety concerns specific to monoclonal antibodies have always related to their inhibition of the biologic target, but there's also been a concern historically with immunogenicity.

As we've moved from mouse antibodies to fully human antibodies, immunogenicity and hypersensitivity have become much less of a concern. With respect to denosumab, it’s a fully human monoclonal antibody. And as Dr. Stehman-Breen commented, we've seen very little evidence of antibodies forming to denosumab, none that neutralize denosumab's activity and we haven't seen any difference in events that code to terms that are typical for hypersensitivity reactions.

Now as noted in FDA's briefing book, the main issue in terms of safety with monoclonal antibodies have been concerns that are attributable to the efficacy in inhibiting the target of therapy and I've given some examples here.

For example, the monoclonal antibody abciximab, which inhibits platelet function, has proved to be very effective in inhibiting thrombosis in cardiovascular disease. But it also has a bleeding risk, so it's clearly an on target effect, but it is a safety concern. Antibodies that have had important therapeutic benefits based on their potent effects in modulating immune responses such as Rituxan and Tysabri, have also turned out to have significant risks. One of the ones recently noted is progressive multifocal leukoencephalopathy, or PML, which is thought to be attributable to impaired immune response associated with the target of these therapies.

Similarly, other monoclonal antibodies have been associated with serious safety concerns and boxed warnings as a consequence of their efficacy in inhibiting their targets, but they remain important

1 therapeutic agents because of their profound efficacy
2 for a critical illness.
3 So what about denosumab? What do we know
4 about RANK ligand inhibition? Dr. Lacey highlighted
5 the preclinical data that supported the development of
6 denosumab. The predominant effect in adult
7 preclinical models and in our clinical development
8 program is the reduction in bone resorption with
9 expected increases in bone mineral density and bone
10 strength. Although there is no evidence of an adverse
11 effect on bone due to long-term inhibition of RANK
12 ligand, it will be important to ensure that there is
13 long-term follow up of patients treated with denosumab
14 to better understand the benefit/risk of long-term
15 inhibition and bone resorption by this mechanism.
16 Now the preclinical data and clinical
17 studies do not suggest a broad immunosuppressive
18 effect of RANK ligand inhibition. Nonetheless, there
19 have been signals of increased infections in patients
20 treated with denosumab. As noted in the briefing book
21 and Dr. Stehman-Breen's presentation, what we know is
22 there does not appear to be an increased risk of

opportunistic or viral infections, which is inconsistent with any impact on cell mediated immunity.

Overall, as we've noted, there are small differences in common bacterial infections, but not with respect to severity, rate of sepsis, or deaths due to infection. These may be due to chance, but with respect to the increased risk of hospitalization due to skin infection, we've had more of a concern since the etiology may reflect factors other than susceptibility to a bacterial infection.

If it is a real signal it is possible that there is a relationship to a skin specific response such as an increased inflammatory response perhaps relating to the signal we saw of increased adverse events of eczema.

Since RANK ligand is expressed in skin immune cells this is possibly an on target effect, we can't exclude that, and Amgen continues to monitor the risk of infection in our clinical trials to determine whether there may be a modest risk related to RANK ligand inhibition.

Now with respect to malignancy, inhibition of RANK ligand is not expected to have any tumor promoting effects. And in our clinical trials, overall there was no statistically significant difference in the overall adverse events of malignancy.

Dr. Stehman-Breen reviewed the results of the safety analysis and the small imbalances observed with some tumor types, which do not suggest an increased risk of malignancy in patients treated with denosumab.

Importantly there was also no increase in deaths related to malignancy and, overall, the rates of malignancy that we observed in this clinical program are within the range expected in the patient populations we studied and when compared to other clinical trials in similar populations.

Finally, the expectation based on preclinical models was, in fact, there was a potential for denosumab to prevent tumor metastasis to bone and that is currently being studied in an extensive placebo controlled clinical program.

In summary, the expected effect of denosumab inhibition on RANK ligand is decreased bone resorption and our clinical data has suggested that there may be an altered skin immune reactivity in some patients.

Now I'd like to turn my attention to risk assessment, because we have a particularly robust program and we take the view that risk assessment continues throughout the life of a drug in the market no matter how comprehensive the clinical development program.

The risk assessment program plan for denosumab also reflects the additional vigilance appropriate for a therapeutic with a novel mechanism of action. This includes additional placebo controlled trials that offer the highest level of evidence for ascertainment of safety signals, long-term follow up of patients that have been in our clinical trials, and proactive safety surveillance.

Now we've studied a wide variety of patients in the clinical trials with denosumab and they're representative of the patient's that we anticipate would be treated in clinical practice. However, we do

note that these were placebo controlled trials, and as a consequence we tended to include lower risk patients at least with respect to fracture risk. However, the benefits of denosumab in terms of fracture prevention, as you've seen in Dr. Stehman-Breen's presentation, were consistent across all subgroups. There were very few exclusions relating to comorbidity, and as we've noted, denosumab was used even in patients with significant renal impairment.

The adverse reactions that we observed are listed here, and, in addition, although not confirmed in the development program, there are adverse events of interest that we think continue to need to be assessed and I'll detail how we propose to do this.

I do want to comment very briefly and specifically on osteonecrosis of jaw or ONJ. We have and continue to use an independent expert panel to evaluate potential cases of ONJ. Although there were no cases observed in the postmenopausal osteoporosis trial or the HALT indication studies, we have observed in the advanced cancer studies, where we use a 12-fold higher dose of denosumab in comparison to zoledronic

acid in those studies, we have observed cases of ONJ. This is consistent with the known risk of ONJ in patient with advanced cancer and our data suggests that inhibition of bone resorption is an important factor. We continue to assess ONJ with this independent panel in all our clinical programs.

The long-term safety in patients with postmenopausal osteoporosis includes extension studies of our Phase 2 and 3 programs. Out of our Phase 2, 216 study, patients will be followed up for up to 10 years; 45 of 150 patients are currently being followed, and I think these studies in particular will be useful in assessing for long-term fracture risk and events of interest that I've highlighted.

There's also an ongoing placebo controlled study in Japan, which is noted on this slide, which also includes an alendronate arm, a much smaller study than our 216 study, but again will provide important safety data and this study will be completed in 2012.

Now we've planned an unusually large postmarketing observational study that I'd like to discuss now and this is part of the safety

surveillance program that's designed to accrue data on up to 380,000 patients over at least five years. The observational study would include accruing both the 380,000 patients who are treated with denosumab and a similar number of patients treated with other therapies, so over 700,000 patients in total.

Now to accomplish this, we've identified several health care databases which I've shown on this slide. We have experience in collaborating with the academic groups that access these databases and we believe we will be able to collect the data that will define whether there are increased events of interest that I've talked about in denosumab compared with other therapies.

Now how do we approach this? Of particular value, for example, are databases such as the Nordic database, which are electronic medical record databases, so in that database one can get x-rays for ascertainment, for example, of an atypical fracture or a subtrochanteric fracture. The specific design of this study and the selection of appropriate database are in progress and will reflect these concerns, and

clearly, as well, how our discussions in terms of the clinical implementation proceed with FDA.

Now observational studies have well recognized limitations in detecting safety signals. Our study recognizes these issues and is focused on assessment of specific safety signals that should be informed by the observational approach. For example, long-term safety surveillance is useful in detecting rare events that would otherwise be unexpected in the population of interest, so the selection of the number 380,000 based on what we call the rule of three means we should be able to detect events down to 1 in 100,000. This is useful if we're looking for unusual malignancies, and as I've highlighted, we may be able to get data on unusual types of fractures.

Another issue with observational studies is that they may be confounded by underlying illnesses and factors that would favor one treatment or another. Nonetheless, useful comparative rates between treatments can be assessed for events such as overall risks of fractures and rates of severe or opportunistic infections. These databases I want to

specifically note are not useful when there are high expected background rates of disease. So for example, cardiovascular disease risk must be assessed as we've done in a randomized clinical trial.

Finally, with respect to malignancies, we can take advantages I've noted in the last bullet of the National Cancer Institute cancer database to compare relative rates in treatment with denosumab long-term, other therapies, to standardized expected rates.

Overall, the combination of long-term follow-up studies, additional clinical trials, and proactive surveillance using these databases provides a comprehensive pharmacovigilance program that will support the use of denosumab in patients with postmenopausal osteoporosis.

Now in patients treated with hormone ablation therapies for breast and prostate cancer, both programs include long-term follow up, as I've highlighted, which is off treatment for the breast cancer patients and on and off treatment in the prostate cancer patients. In postmenopausal women

treated with aromatase inhibitors for breast cancer, there was considerable interest as we've discussed in determining whether the preclinical data suggesting a benefit in terms of breast cancer outcomes could be confirmed clinically.

The Phase 3 study I've shown on this slide is being carried out by the Austrian Breast Cancer Study Group and it's designed to answer these questions. This study has enrolled 1200 of 2800 patients who will be followed for at least six years for the primary outcome of fracture prevention, but in addition there are endpoints related to the risk of cancer recurrence.

The cataract issue requires a dedicated study, and since we did observe cataracts in men treated with androgen deprivation, we have designed and have initiated a dedicated ophthalmologic study, which is placebo controlled, and in the at risk population and will be completed by 2011 to definitively assess this risk.

I would like to now briefly comment on another important aspect of Amgen's overall

development program for denosumab, but independent of the program we're discussing today. Because bone resorption is required in the progression of metastatic bone disease, denosumab is being studied in patients with advanced cancer with bone metastasis.

Phase 2 studies identified the appropriate dose for these Phase 3 studies as a 12-fold higher dose of denosumab in terms of its efficacy. This is what is being tested and compared with zoledronic acid in the three studies I have illustrated on this slide.

The breast and solid tumor studies recently completed, and we did disclose these, the analysis is still ongoing, I've simply highlighted from a safety perspective that the overall survival in these studies compared to the zoledronic acid for patients treated with denosumab was similar. And as I've noted, these patients were treated with a dose that's, in this case, of a 120 milligrams Q monthly subcutaneously. I do want to highlight that these data have not yet been reviewed or submitted to FDA.

In addition, based on our preclinical data, denosumab is being studied at the higher doses in

prevention of bone metastasis in placebo controlled studies of prostate and breast cancer patients. The prostate study is fully enrolled, that's the second one from the bottom, and will complete four years of follow-up next year and report out. The breast cancer study is planned to start later this year, and these studies will provide additional data of denosumab effects on at least tumor progression as it relates to general tumor outcomes.

So to summarize, the benefit/risk of denosumab in patients with cancer to prevent complications of bone loss is supported by additional studies and other programs characterizing higher doses of denosumab to treat patients with metastatic bone disease.

I'd like to now turn my attention to the minimization of potential risk through risk communication to prescribers and patients. Risk communication is the foundation of risk minimization. With respect to the risks of denosumab in the clinical development program, there are safety issues that can be minimized through labeling. The most important is

hypocalcemia, which while expected for an antiresorptive agent has the potential to be clinically meaningful. Therefore labeling should contraindicate use in patients with uncontrolled hypocalcemia and would recommend Vitamin D and calcium supplementation in patients who are treated with denosumab.

Although ONJ has not been observed in this clinical program, it is a potential serious risk that has been a concern with bisphosphonates and has been observed in the advanced cancer studies. There is evidence that communication of this risk and the need for good dental hygiene may be of value in minimizing risks. The risk of hospitalization with skin infections is also amenable to risk minimization through labeling.

Other risks that have been observed clearly need to be communicated, recognizing that communication may not minimize the risk. Similarly, communication of theoretical risks in some instances may be appropriate, but only to inform prescribers and patients, not to minimize risk. Amgen is committed to

working closely with FDA to develop the appropriate risk communication plan.

In terms of clinical use, there are several aspects I want to highlight. Denosumab is administered as a 60 mg subcutaneous injection every six months. Dosing adjustments are not required, and in contrast to some of the bisphosphonates, denosumab can be used with significant renal dysfunction. Injections of denosumab are well tolerated and not associated with acute reactions.

Denosumab should be administered by health care professional to ensure the full dose is properly injected. Administration in this manner supports oversight by physicians of adherence to the prescribed six month regimen, which is important since the benefits of denosumab are reversible.

Amgen plans to support patients and prescribers with reminder systems to facilitate adherence. It's also important to note that in clinical trials, dosing of denosumab could occur one month prior or after the six month prescribed injection date, so there is flexibility in scheduling

treatment. Amgen also plans to support patient adherence once they've started on denosumab with an assistance program as appropriate.

Now we've presented a great deal of data from a comprehensive program that led to the development of denosumab as a therapeutic agent. We recognize that there are some areas of scientific controversy with respect to RANK ligand biology, but our data are clear with respect to the benefits in reducing bone resorption, increasing bone mineral density, and preventing fractures.

We look forward to the opportunity to further review the data we've presented with the committee. With respect to the indications we're seeking, the data demonstrated benefit for the prevention of osteoporosis and fractures in women with postmenopausal osteoporosis, supporting the treatment and prevention indications. And as Dr. Siris noted, postmenopausal osteoporosis represents an important health care concern for women, for which there remains a need for alternative therapies, one that denosumab can satisfy.

The overall safety profile of denosumab compares favorably to other approved classes of agents for these indications and efficacy in some instances appears superior. In postmenopausal women with breast cancer treated with aromatase inhibitors, clinicians have recognized the need to prevent bone loss associated with treatment and there are no currently approved therapies.

In men with prostate cancer with androgen deprivation, the impact of bone loss and fractures on patient outcome has also been recognized. In both populations, denosumab demonstrated efficacy in reducing bone loss and in the prostate cancer patients in preventing fractures.

In addition to the programs supporting the regulatory requirements for approval for these indications, we have ongoing and planned studies and a pharmacovigilance program that will support the benefit/risk of denosumab long-term.

We appreciate the opportunity to review our data with you and look forward to the panel's comments. Thank you.

DR. CARSON: Thank you very much and thank your whole team for the excellent materials you've prepared for us and a very organized presentation today. Also, I hope you'll express and extend our appreciation to those many, many clinical investigators who helped you gather your data. And maybe the press can help us all today thank those thousands of men with prostate cancer, hundreds of women with breast cancer, and many, many postmenopausal women with bone loss who three years ago and more took an unknown risk for an unknown benefit and donated a lot of their time to help the team present this data today.

Now we will take a short break. Committee members please remember there should be no discussion of any of the meeting topics during the break amongst yourselves or any members of the audience. We'll resume at 10:05. Thanks.

(Whereupon, a recess is taken.)

DR. CARSON: The FDA's presentations will begin with Dr. Popat.

DR. POPAT: Welcome back. I am Vaishali

Popat. I am a medical officer at FDA in the Division of Reproductive and Urologic Products. I will present the FDA analysis on the notion of efficacy.

The focus of our efficacy and safety presentations includes the Dose-Finding Trial 223, the primary efficacy trial for each of the four indications and Trial 234, which evaluated patients previously on alendronate, who were switched to denosumab or continued on alendronate. We will be discussing only safety issues with Trial 234.

Prior to discussing individual primary efficacy trials, I will briefly talk about pharmacometric profile and dose selection. The pharmacometric profile of denosumab has been evaluated, and it reveals that denosumab is 61 percent bio-available. The half-life is 25 days. There is no accumulation.

Similar pharmacokinetic profile is observed across different population groups. The PK profile is not affected by age, weight, gender, race or renal function. And pharmacokinetic analysis showed that a single dose is adequate -- single fixed dose is

adequate. Weight did not affect the fracture or BMD efficacy.

So the Trial 223 is a dose-finding trial. This was a four-year randomized placebo and active control trial of postmenopausal women with low bone mass. The primary efficacy endpoint was lumbar spine BMD at 12 months. Nine treatment cohorts were evaluated with 40 to 50 subjects per cohort. These cohorts were placebo; denosumab 6 milligrams, 14 milligrams or 30 milligrams Q3months or 14 milligrams, 60 milligrams, 100 milligrams and 240 milligrams Q6months, and 70 milligrams alendronate once weekly. The 70 milligrams once weekly alendronate dose is the dose for treatment of postmenopausal osteoporosis.

The annual population was predominantly Caucasian with mean age of 63; 64 percent of those enrolled completed the trial.

The results of the primary efficacy endpoint of change in lumbar spine BMD are presented in this table. The dose groups are arranged by the yearly dose received. All those groups achieved increased

lumbar spine BMD at month 12. The 100 milligrams Q6months and 210 milligrams Q6months did not achieve better BMD response than the 60 milligrams Q6months. The sponsors selected only one dose, 60 milligrams Q6months, highlighted in this light blue to take into Phase 3.

The primary efficacy trial for the treatment of osteoporosis indication is Trial 216. This was a randomized, double-blind, placebo-controlled, three-year trial in postmenopausal women with osteoporosis. The primary endpoint was subject incidence of new morphometric vertebral fractures at three years. Secondary endpoints were timed to first nonvertebral fracture and time to first hip fracture. Important tertiary endpoints were change in lumbar spine and hip BMD.

Overall, 7,808 subjects were randomized; 46 subjects did not receive investigational product, and 86 percent of the population completed the trial.

The trial participants were predominantly Caucasian with a mean age of 72 years. The baseline lumbar spine BMD T score were minus 2.8 and 23 percent

of the population had a vertebral fracture at baseline. A post hoc analysis doing the FRAX calculator was performed and 10-year major osteoporotic risk for the fracture was 19 percent, and 10-year hip fracture risk was 7 percent.

For the primary efficacy endpoint of new vertebral fractures, treatment with denosumab demonstrated 4.8 percent absolute risk reduction and 68 percent relative risk reduction at month 36 with a p-value of less than 0.001.

For the secondary efficacy endpoint, nonvertebral fracture, treatment with denosumab resulted in 1.5 percent absolute risk reduction and 20 percent relative risk reduction with a p-value of 0.0106.

For another secondary endpoint, hip fractures, the treatment with denosumab resulted in .3 percent absolute risk reduction and 40 percent relative risk reduction. The relative risk reduction p-value was 0.036. It should be noted that for the absolute risk reduction, the confidence interval crosses zero.

In the ongoing review, to evaluate this further, we looked at the incidence of hip fractures for each year of the study. So this slide shows the accrued incidence of hip fractures within each one-year time interval of this three-year study. It's not a cumulative incidence.

So it's noteworthy that in year 1 and 2 -- in year 1, the placebo incidence is .5 and denosumab is .3. So denosumab is lower than placebo. In year 2, it's .4 versus .1. So again, it's lower than placebo. However, in year 3, the incidence climbs back to the similar rate as placebo.

We recognize that the number of fractures is small, but because of this hip fracture finding noted in year 3, we looked further to see if the same trend occurred with nonvertebral and vertebral fractures.

So this slide shows the accrued incidence of nonvertebral fractures and vertebral fractures. Again, this is by year. It's not a cumulative incidence. So incidence of nonvertebral fracture was greater in placebo group from all time intervals compared to denosumab. And there was no change in the

new nonvertebral fracture incidence rates between year 2 and year 3.

For vertebral fractures, the incidence was greater in placebo group in all three years compared to placebo. We also note that the incidence of new vertebral fractures was similar in year 1 and 2. In year 3, the incidence was higher than 1 and 2.

Although a tertiary endpoint, the changing BMD at lumbar spine and total hip, they're an important endpoint to discuss. And it is the primary endpoint for all the other trials to be discussed today.

At the lumbar spine, the treatment difference at month 36 was 8.8 percent increasing BMD, and for total hip, the treatment different at month 36 was 6.4 percent increase in BMD. These numbers come from the whole trial population, not the substudy.

Another supportive measure of efficacy are bone turnover markets. CTX is a market of bone resorption. This graph outlines the percent change in CTX levels over time. Treatment in denosumab resulted in marked suppression of serum CTX levels. The nadir

in CTX appears to occur one to three months following the denosumab dose, a time when denosumab effect is likely maximal. Before the next dose, CTX levels begin to trend back towards baseline.

Bone remodeling includes bone resorption and bone formation. Bone resorption and bone formation are tightly coupled processes. With denosumab therapy, the marker of bone formation, P1NP, lagged behind CTX but followed a similar pattern.

In our evaluation of the CTX effect, it was noted that some patients had levels of CTX that were undetectable or below the lower limit of quantification. This finding was most notable at the anticipated time of maximal denosumab effect. In this table, the blue highlighted columns represent the visits one, two, three months following denosumab doses, a time at which the nadir occurs.

At these time points, CTX was undetectable in 39 to 68 percent of subjects treated with denosumab. Similarly, the marker of bone formation, P1NP, was also undetectable in 24 to 36 percent of the subjects treated with denosumab at month 6 onward with

the highest number of subjects with undetectable levels at month 36.

In their evaluation of the person's changing CTX, the sponsor said the CTX level for subjects with undetectable levels to the lower limit of quantification was 0.049. We were concerned that this approach may underestimate CTX suppression in subjects treated with denosumab. So we conducted an evaluation of change in CTX based on three scenarios: one, undetectable CTX levels set to the lower limit of qualification which is 0.049 in the blue line. The red line represents the CTX levels set to half the lower limit of quantification which is 0.025 and the green line represents undetectable levels set to zero.

So this graph shows the results for the change in CTX with denosumab therapy in the first year of the trial based on these three scenarios. From this analysis, we can only conclude that the decrease in serum CTX levels one month after denosumab dosing was in the range of 87 percent to 94 percent. It should be noted that this degree of suppression of bone resorption markers has not been seen before with

any other anti-resorptive agent.

Trial 132 was the primary efficacy trial for the osteoporosis prevention indication. This was a randomized, double-blind, placebo-controlled, four-year trial with two years of active treatment and two years of follow-up off treatment in postmenopausal women with low bone mass. The primary efficacy endpoint was person changed from baseline in lumbar spine BMD at 24 months. Secondary endpoints were persons changed from baseline in BMD of the hip, distal radius and total body.

Overall, 332 subjects were randomized. Three subjects did not receive investigational product, and 87 percent of the population completed the trial.

The baseline characteristics of the population enrolled in this trial reflect the intended population for the prevention of osteoporosis indication. They are younger women. The mean age is 59 years with a bone mineral density that is low but not in the osteoporotic range. These subjects don't have a history of osteoporotic fracture and because of

their young age, their fracture risk tends to be low.

In this population, the treatment difference at month 24, which was the primary efficacy endpoint, for lumbar spine following the denosumab therapy was 7 percent. Total hip was the secondary efficacy endpoint, and the treatment difference at month 24 was 4.5 percent with a p-value of less than 0.001.

With many therapies that are used for treatment of chronic disease, such as osteoporosis, the durability of effect after cessation of therapy is important to understand. In Trial 132, subjects were on therapy for the first two years and then followed off therapy for the last two years. This graph shows change in bone mineral density from baseline across this four years.

During the first two years of the treatment, lumbar spine BMD increased continuously. However, off treatment, it rapidly returned to baseline in the next two years. The same thing happened for the total hip BMD.

We looked at the BMD results. The fracture is also an important -- it's actually the main

interest. So we also looked at the fracture incidence during this off treatment phase because of the rapid decline in the BMD. So the number of fractures occurring the off treatment phase was small. There were five fractures in the placebo group and nine fractures in the denosumab group.

Trial 135 is the primary efficacy trial for the prevention and treatment of bone loss in patients undergoing hormone ablation for breast cancer indication. This trial was randomized, double-blind, placebo-controlled, four-year trial with two years active treatment and two years off treatment in women receiving aromatase inhibitor therapy for breast cancer who have low bone mass.

The primary efficacy endpoint was person changed from baseline in lumbar spine BMD at 12 months. Secondary efficacy endpoints were person changed from baseline in BMD of the hip, distal radius and total body. Exploratory efficacy endpoint included overall survival at month 24.

A total of 252 women were randomized. Three subjects did not receive investigational product, and

81 percent completed the trial. Subjects were predominantly Caucasian and similar to the osteoporosis prevention population. The breast cancer population mean age was 59 years.

Bone mineral density was minus 1.1 at lumbar spine. Only 1 percent of the population actually met the criteria for osteoporosis at baseline. The baseline characteristics of the breast cancer include time since diagnosis of three years and 65 percent have been on aromatase inhibitor therapy for at least six months.

Most subjects had Stage 1 or 2 cancer based on American Joint Committee on Cancer Criteria; 98 percent has estrogen receptor positive tumor while 83 percent were progesterone receptor positive. HER2/neu status was negative in 65 percent of patients. The history of prior breast cancer therapies were well balanced between the groups.

In this population, the treatment difference at month 12, which was the primary efficacy endpoint, following the denosumab therapy was 5.5 percent at lumbar spine and 3.7 percent at total hip.

Trial 138 is the primary efficacy trial for the prevention and treatment of bone loss in patients undergoing androgen deprivation therapy for prostate cancer indications. This was a randomized, double-blind, placebo-controlled, five-year trial with three years active treatment and two years off treatment in men undergoing androgen deprivation therapy for prostate cancer.

Enrollees were either more than or equal to 70 years of age or if they were less than 70 years, then they would have to have low bone mass or a history of osteoporotic fracture.

The primary endpoint was person changed from baseline in lumbar spine BMD at 24 months. Secondary endpoints were person changed from baseline in BMD of the hip, incidence of any fracture, incidence of new morphometric vertebral fracture. Exploratory endpoint included overall survival at month 36.

A total of 1468 men were randomized. Twelve subjects did not receive investigational product, and 62 percent completed the trial. Trial participants were predominantly Caucasian with the mean age of 75

years. Bone mineral density was normal. Recall that in this trial, patients were eligible for enrollment if they were over age 70, regardless of their BMD status; 83 percent of the subjects were over age 70; 23 percent had a vertebral fracture at baseline. Mean duration of androgen deprivation therapy was 33 months.

The baseline characteristic of the prostate cancer include a mean time since diagnosis of five years. Most subjects had Stage 2 cancer based on National Comprehensive Cancer Network scoring and a Gleason score of 7 or below. Approximately half did not receive primary cancer therapy. History of radiation surgery and chemical castration were similar in both groups.

In this population, treatment difference at month 24, which is the predefined endpoint, following denosumab therapy was 6.7 percent at lumbar spine and 4.8 percent at total hip. Treatment with denosumab demonstrated a 2 percent absolute risk reduction and 28 percent relative risk reduction in any fracture. This was not significant. However, for new vertebral

fracture, the treatment with denosumab resulted in 2.4 percent absolute risk reduction and 62 percent relative risk reduction, and this was with a p-value of 0.0125.

So in summary, for fracture efficacy, denosumab 60 milligrams every six months was effective in decreasing the incidence of fractures in postmenopausal osteoporotic women. However, we note the incidence of hip fracture was lower than placebo in the first and second year but became similar to placebo in the third year of the primary fracture trial.

For the BMD, treatment with denosumab resulted in increase in the populations evaluated, including postmenopausal women with osteoporosis and low bone mass, women with low bone mass receiving aromatase inhibitor therapy for breast cancer, and men undergoing androgen deprivation therapy for prostate cancer.

There is profound suppression in markers of bone resorption. Once treatment with denosumab is discontinued, BMD quickly returns to baseline.

Now, I will turn the podium over to my colleague, Adrienne Rothstein, who will present the safety analysis.

DR. ROTHSTEIN: Good morning, my name is Adrienne Rothstein. I'm a clinical reviewer in the Division of Reproductive and Urologic Products, and I'll be presenting the FDA's safety analysis of denosumab.

For this safety analysis, we reviewed case narratives, adverse events terms reported by the investigator and reviewed the medical coding by the applicant. We also had assistance from our specialized quantitative safety pharmacoepidemiology team to help evaluate adverse events of special interest.

Throughout this safety review, serious adverse events or SAEs refers to adverse events that meet the regulatory definition of serious, which is defined as an event that results in any of the following outcomes: death, life-threatening life adverse event or inpatient hospitalization or prolongation of existing hospitalization, persistent

or significant disability or an important medical event that required an intervention to prevent these serious outcomes.

Our safety review focused on four primary key studies, 216, 132, 135 and 138, which have been previously described. The PMO safety population included 8,091 subjects. The HALT safety population included 1,705 subjects.

When we look at overall adverse event rates for the primary postmenopausal osteoporosis trials, the number of deaths in the placebo group was higher than in the denosumab group in Trial 216, and there were no deaths in Trial 132. Serious adverse events were balanced in Trial 216; however, denosumab subjects in Trial 132 had a higher incidence of serious adverse events. Adverse events that led to trial withdrawal or investigational product discontinuation and overall adverse rates did not differ between the treatment groups for either trial.

In the primary hormone ablation trials, deaths were balanced across both treatments groups. There was a higher rate of serious adverse events in

subjects receiving denosumab in both trials. The incidence of adverse events that led to withdrawal from the trial, discontinuation of investigational product and the overall adverse event profile were similar across both treatment groups in these studies.

Deaths in the Phase 1 trials were examined. All deaths in Phase 2 trials were also examined except for trials in patients with advanced cancer. There were two deaths in Phase 1 trials in subjects receiving denosumab, including an accidental death and cancer progression in a breast cancer patient.

In the Phase 2 Dose-Finding Trial 223, there were four deaths in the denosumab group, one from a cerebrovascular accident and three neoplasms. All three neoplasms occurred in the denosumab 100 milligrams Q6months cohort. In the extension phase of this dose-finding study, there was one additional death, cause unknown.

In the pooled osteoporosis safety database, there were 90 deaths in the placebo group and 70 in the denosumab group. The most common causes of death were neoplasms, cardiac disorders, respiratory

disorders and nervous system events.

In the pooled hormone ablation safety database, deaths were balanced across the two treatment groups. The most common causes of death were cardiac disorders, respiratory disorders, nervous system events and neoplasms. There were no imbalances in the denosumab groups in deaths in any of the Phase 3 trials.

In terms of serious adverse events in Trial 216, which is the PMO treatment, the overall incidence of serious adverse events, which here includes fatal events, was balanced between the treatment groups. The incidence of cardiac, musculoskeletal infection and neoplasm systems were -- these events were increased in the denosumab group. In the placebo group, the incidence of serious adverse events was higher in the injury system organ class, which was driven by more fractures in this group.

In Trial 132, the PMO prevention trial, the denosumab group had more serious adverse events of infection and neoplasm. There were eight subjects on denosumab who developed serious infections while only

one placebo subject developed a serious infection. There was also an imbalance in neoplasms in this trial.

In both hormone ablation trials, the incidence of all serious adverse events was higher in the denosumab as compared to placebo. In Trial 135 in breast cancer patients, the denosumab group had more serious musculoskeletal and neoplasm events. In Trial 138 in prostate cancer patients, the most common serious adverse events were in the cardiac, nervous, neoplasms and infection systems. These were similar to what was observed in the PMO trials.

When we look at adverse events, common adverse events leading to discontinuation of investigational products in the postmenopausal trials, we see that approximately the same number of subjects in each treatment group discontinue treatment because of an adverse event. In the denosumab group, the most common adverse events there were reported as the reason for investigational product discontinuation were breast cancer, back pain and constipation. In the placebo group, lumbar and thoracic vertebral

fractures, breast cancer, back pain and constipation were the most common adverse terms that led to treatment discontinuation.

The next portion of my presentation will focus on the adverse events of special interest listed here. In some cases, these events are specific to the denosumab safety database while others are evaluated with all anti-resorptive therapies.

Our safety review evaluated infections. I'll present an overview of infections in each of the four primary Phase 3 trials and then focus on specific infections with imbalances between the treatment groups.

There were several reasons to investigate infections thoroughly. As previously mentioned, denosumab is an inhibitor of the RANK ligand. RANK and RANK ligand maybe involved in B and T cell differentiation and dendritic cell survival and may also play a role in ongoing antigen surveillance.

There is an early signal for infections. In Phase 1 studies, three subjects required hospitalization for pneumonia after a single dose of

denosumab. One of these subjects was subsequently diagnosed with lung cancer which could have contributed to the event. In the other two subjects, who were males less than 35 years old, no significant medical history was reported.

In Phase 2 trials in Trial 223, serious adverse events related to infection occurred in 3 percent of denosumab subjects and none of the placebo or alendronate subjects.

The incidence of serious infections in subjects receiving denosumab was higher across all four Phase 3 primary trials in four different populations. The overall incidence of any adverse event, which would include serious and non-serious, was not higher in the denosumab group for the osteoporosis trials.

For the hormone ablation trials, the overall incidence of any event of infection was higher in the denosumab group. There were no imbalances in opportunistic infections between the treatment groups.

The main imbalance in serious events of infection is related to skin infections. Serious skin

infections that occurred in Trial 216 are shown here. These subjects were hospitalized for their infections. Erysipelas and cellulitis were more common in the denosumab group.

Trials 132 and 135 each had one denosumab subject with a serious adverse event of cellulitis while there were none in the placebo group. However, the number of serious skin infections were balanced in Trial 138 across treatment groups.

Additional imbalances were noted in serious ear infections and urinary tract infections. For serious ear infections in Trial 216, no placebo subjects had an event of this nature while five denosumab subjects had events coded to this event category. This included four events of labrynthitis and one event of otitis media.

Serious urinary tract infections occurred in 17 placebo subjects in Trial 216 and 28 denosumab subjects in Trial 216. These events were balanced in Trial 138 across the two treatments groups.

In Trial 216, it was noted that there were three cases of endocarditis in the denosumab group and

none in the placebo group. One denosumab subject died and another subject received a valve replacement.

Based on a 2001 article in the New England Journal of Medicine, the incidence rate of native valve endocarditis in 1.7 to 6.2 cases per 100,000 person years. In this trial, in Trial 216, the exposure was approximately 11,000 person years. So the number of endocarditis cases reported in Trial 216 was at least fourfold higher than would have been anticipated based on this article.

There were eight subjects who had adverse events coded as infective arthritis. The majority of these patients received oral antibiotics, and there were no serious events reports.

In summary, there was an imbalance in the number of serious infections in the denosumab group. Most notable were infections of the skin, ear and urinary tract. An imbalance in endocarditis was noted, although the event occurred rarely. An imbalance in infective arthritis was noted, although all events were non-serious. There was no evident increase in opportunistic infections.

New malignancies were also investigated in the denosumab primary PMO trials. Normally, pharmacology and toxicology studies in animals are conducted to evaluate carcinogenicity. However, this antibody is specific to human and nonhuman primate RANK ligand and is not active in rodents. Therefore, no carcinogenicity studies were performed due to a lack of an animal model.

In the Dose-Finding Trial 223, as previously mentioned, there were three deaths due to neoplasms in the 100 milligrams Q6months cohort. In this cohort, 42 subjects were randomized and 41 subjects received at least one dose of denosumab. An additional observation was that breast cancer was a common adverse event leading to investigational product discontinuation in the primary PMO trials.

There were more new events of neoplasm in the denosumab group in the primary PMO trials. This number includes malignant, benign and unspecified conditions. When benign conditions were removed, there was a higher incidence of malignant or unspecified conditions in subjects receiving

denosumab.

What is presented here is any imbalance of 0.2 percent or greater in the reported event incidence between the two treatment groups. In particular, there were more gastrointestinal, breast and reproductive malignancies in the denosumab group. However, there were more respiratory malignancies in the placebo group.

In summary, no carcinogenicity studies were performed due to a lack of an animal model. In the dose-finding trial, three subjects in a high dose denosumab group died of a new neoplasm. In the primary PMO studies, there was an imbalance in the incidence of malignancies in the denosumab group driven by breast, reproductive and gastrointestinal cancers. The significance of these findings is unclear.

Tumor progression was specifically evaluated in the breast and prostate cancer trials which enrolled subjects with non-metastatic cancer. These hormone ablation trials were not designed to evaluate cancer outcomes. However, we noted there was an

imbalance in metastatic events in Breast Cancer Trial 135 with 4.2 percent of placebo subjects and 7 percent of denosumab subjects experiencing metastatic events. And in Trial 138, in prostate cancer subjects, 5.5 percent of placebo subjects and 8.2 percent of denosumab subjects had metastatic events.

Our quantitative safety team noted that there was a statistically significant difference between treatment groups in the event category dermatitis and eczema and the event category rashes, eruptions and exanthems for the primary PMO trials. Based on this exploratory finding, dermatologic adverse events were investigated.

There was an imbalance in adverse events related to skin and soft tissue disorders. This grouping does not include skin infections. These dermatologic adverse events were not specific to the injection site. They were mainly driven by the grouping of epidermal and dermal conditions, which is the top line with 8.4 percent of placebo subjects and 11 percent of denosumab subjects experiencing these events.

This event grouping includes several events, but the specific events that had a higher incidence in the denosumab group were dermatitis and eczema with 2 percent versus 3.6 percent, pruritis with 2.4 percent versus 2.7, and then rashes, eruptions and exanthems with 2.2 percent in placebo and 2.9 percent in the denosumab group.

Skin serious adverse events occurred in seven placebo subjects and 10 denosumab subjects in Trial 216. All these subjects were hospitalized for the event. In many of these cases, while denosumab could not be ruled out as the cause, subjects were noted to be on other medications that could also have contributed to the event. In addition, there were four cases that were categorized as -- the investigator reported it as toxic skin eruptions that were reported in Trial 216. These cases were reviewed and do not appear to be secondary to denosumab.

Although a subset of the skin events that were investigated had contributory factors, we continue to be concerned about the imbalance between the two treatment groups for epidermal and dermal

adverse events.

Pancreatitis was evaluated because of an imbalance in acute pancreatitis noted in Trial 216. There were a total of four placebo subjects and eight denosumab subjects in the primary PMO trials that had events of pancreatitis. There was only one subject in the placebo group with a serious adverse event while all the events in the denosumab group were serious.

There was no obvious temporal relationship between investigational product exposure and the development of these events and many of these cases were confounded. However, there were two noteworthy cases from the PMO primary trials that I will describe. A 74-year-old subject who had been receiving denosumab for two years developed pancreatitis 17 days after her last dose of denosumab. The investigator stated that the woman had no known risk factors for pancreatitis.

There was another case where a family reported that a 71-year-old subject died of acute pancreatitis in month 4 of the study. The family refused to disclose further information or provide any

records.

However, when we look at Trial 138, we see there are more cases of pancreatitis in the placebo group with four events than in denosumab subjects. Only one case was reported in denosumab. We are unclear of the significance of this imbalance noted specifically in the primary PMO trials nor of the two noteworthy cases that were previously described.

Because of the imbalance noted in cataracts in the prostate cancer trial, ocular adverse events were reviewed. Trial 138 enrolled men with a mean age of 75 years. Trial 216 enrolled women with a mean age of 72 years. The imbalance in cataracts was noted in Trial 138. However, this imbalance was not seen in Trial 216.

For Trial 138, 1.2 percent of subjects on placebo and 4.7 percent of subjects on denosumab developed cataracts. Only two of these were serious in the denosumab group. For Trial 216, 6.3 percent of placebo subjects and 5.7 percent of denosumab subjects developed cataracts. The number of these that were serious was 0.7 percent in the placebo group and

0.5 percent in the denosumab group.

It should be noted that the incidence of adverse events in the placebo group for Trial 138 was lower than the incidence seen in Trial 216. There was no notable imbalance between treatment arms in other ocular adverse events that were reviewed.

The significance of this imbalance in the incidence of cataracts in Trial 138 is unclear at this time. As mentioned, the sponsor has proposed a randomized placebo-controlled clinical trial to evaluate the risk of cataracts in men with prostate cancer receiving androgen deprivation therapy.

Cardiovascular adverse events are common in the age groups enrolled in the denosumab trials and were thoroughly evaluated. Osteoprotegerin is a cytokine and a TNF receptor superfamily. Its main function is inhibition of the RANK ligand and osteoclass differentiation. Literature reports suggest an association between osteoprotegerin levels and arterial wall calcification, cardiovascular disease and mortality. There is a theoretical potential for elevated osteoprotegerin levels with

denosumab inactivation of RANK ligand as it binds to the same target.

There was a specific evaluation of cardiac events which included the following: death and cardiovascular serious adverse events from Studies 216 and 138 were adjudicated by an independent panel of cardiologists that were assembled by the sponsor. There was a similar incidence of cardiac deaths and serious adverse events that were positively adjudicated in the treatments arms.

Osteoprotegerin levels were measured in a substudy of Trial 216. Osteoprotegerin levels did not increase with denosumab use. Abdominal aortic calcification scores were assessed using the x-rays that had been collected for fracture analyses. No differences in abdominal aortic calcification scores were seen. Therefore, while the methods used to assess cardiovascular safety do have limitations, there's no clear cardiovascular safety signal based on the available data.

Hypocalcemia is an event that's closely evaluated with all anti-resorptive therapies.

Hypocalcemia occurs with the anti-resorptive therapy because these therapies essentially function to shut off bone as a reservoir for calcium. All subjects in the primary Phase 3 trials were supplemented with calcium and Vitamin D. Timing of the calcium measurements in these primary Phase 3 trials was at one month, which missed the anticipated calcium nadir which is eight to 11 days post-dose.

One denosumab treated subject in Trial 138 reported a serious event of hypocalcemia. In the Phase 3 PMO trials, 1.6 percent of subjects had an asymptomatic corrected calcium level less than 8.5. Corrected calcium levels less than 7.5 were rare.

Osteonecrosis of the jaw is an adverse event of interest for all anti-resorptive therapies. osteonecrosis of the jaw may be associated with inhibition of bone remodeling. Potential cases of ONJ were adjudicated by an independent committee assembled by the sponsor. There were pre-specified search criteria to identify potential cases of osteonecrosis of the jaw.

There was a balanced distribution of these

potential cases that were sent to the committee for adjudication. No cases met the definition of ONJ. Cases of ONJ, however, are being reported in denosumab subjects in ongoing and completed advanced cancer trials.

Immunogenicity is the last topic that I'll be presenting. Therapeutic proteins have the potential to elicit an immune response. A three-step process for detection of antibodies to denosumab was used, a screening immunoassay to detect binding antibodies, a second immunoassay to confirm binding antibodies and a cell-based bioassay to evaluate for the presence of neutralizing antibodies. Most clinical studies from the denosumab program had evaluations of immunogenicity.

Binding antibodies to denosumab were measured in subjects with postmenopausal osteoporosis, cancer and other conditions such as rheumatoid arthritis. In these subjects exposed denosumab, the presence of pre-existing binding antibodies was identified in 0.1 percent to 0.5 percent of subjects while 0.5 percent to 1.1 percent had binding

antibodies according to these assays used.

When the placebo and active control subjects were looked at, 0.2 percent of these had binding antibodies present, pre-existing binding antibodies were present, while 0.3 percent were identified later. These subjects were never exposed to denosumab. The significance of these binding antibody assays is unclear at this time.

The last speaker for the FDA this morning is Dr. Theresa Kehoe.

DR. KEHOE: Thank you. I'll be presenting the findings for the bone histomorphometry studies and then will provide a summary of the denosumab safety, and then conclude with a discussion of FDA's risk benefit assessment.

Evaluation of bone biopsy specimens is a required safety evaluation for agents seeking a treatment of osteoporosis indication. Two types of evaluations occur on these bone biopsy specimens. one is to evaluate for evidence of pathologic histology and the second is quantitative histomorphometry, which allows for tissue level assessment of bone turnover

and bone mineralization.

Abnormalities of bone mineralization has been a focus with bisphosphonate drugs as these drugs are incorporated into the pyrophosphate crystals when bone is mineralized.

When we talk about bone histology, recall from the slide presented by Dr. Stehman-Breen earlier this morning that there are two types of bones. First you see trabecular or cancellous bone, which is the sponge-like bone in the contact with the marrow space. It is metabolically active and rapidly turned over. Cortical or compact bone is the denser or outer envelope of bones, and it's found on all bones.

In general, the bone biopsy specimens revealed normal lamellar bone and normal bone mineralization. The following abnormalities were noted. Five subjects in Trial 216 did not have osteoid that could be visualized at month 24. Osteoid is unmineralized new bone matrix. This may be evidence of over suppression of bone turnover such that no new bone is being formed.

One subject in Trial 216 had normal

histology at month 24 but had developed endosteal resorption of cortical bone at month 36. Endosteal resorption of cortical bone or increased bone resorption on the inside surface of cortical bone, this finding can be associated with reduced bone strength. In addition, one subject maintained on alendronate in Trial 234 had evidence of marrow fibrosis.

Quantitative histomorphometry evaluation requires labeling the bone to enable measurements of bone resorption and bone formation. Because it is taken up by newly mineralized bone and fluoresces under polarized light, tetracycline or its congeners are used to label bone. In this discussion, the agents. whether tetracycline or demeclocycline, used to label bone are referred to as tetracycline.

Subjects in the bone biopsy substudies received two timed spaced courses of tetracycline. The presence of two lines of labeling or tetracycline double label provides evidence of active bone remodeling and formation. Trabecular double label is necessary to full assess quantitative histomorphometry

parameters. If double tetracycline labeling is not seen on the trabecular bone in the measurement field, then an extended label search can be conducted and includes a search for single or double tetracycline labeling in all of the trabecular and cortical bone fields.

Outlined in this table are the results from the extended label search for the bone biopsy samples from Study 234, which is the bisphosphonate switch study, and Trial 216, the postmenopausal fracture study. The first row shows the number of biopsy samples that were obtained in these studies, month 12 for Study 234 and both month 24 and 36 for Study 216.

All samples obtained from placebo and alendronate subjects had either -- they had label present that was either single label or double label on the extended label search. However, for biopsy samples obtained from subjects transitioning from alendronate to denosumab in Study 234, 20 percent had no label at month 12. In Trial 216, no label was present in 35 percent of the biopsy specimens obtained at month 24 and 38 percent of the biopsy specimens

obtained in month 36.

Full evaluation of all static and dynamic histomorphometry parameters require the presence of double tetracycline labeling in the histomorphometry measurement field. Any label and no label rows at this table show the presence of any label seen on extended label search or anywhere in that bone biopsy. The last line, the full evaluation row here, shows the number of samples that had double tetracycline label in the trabecular measurement field and were available for full assessment of bone histomorphometry parameters.

What we can see in this last row is that a full evaluation was possible for all biopsy specimens from alendronate-treated subjects and 40 percent of denosumab-treated subjects in Trial 234 at month 12. In Trial 216, a full evaluation was possible in 84 percent of subjects who received placebo at month 12 and 16 percent of subjects who received denosumab at month 24. In Trial 216 at month 36, 88 percent of placebo subjects and 10 percent of denosumab treated subjects had the availability of

having a full assessment of bone histomorphometry.

One question that may be asked is how does this compare to other agents that have previously been reviewed for the same indications. In those samples, the rate of fully evaluable bone biopsies is 50 percent of higher.

The results of the quantitative histomorphometry parameters are outlined in the briefing document. In Trial 216, at month 24 and 36, parameters of bone resorption were significantly decreased. In some evaluable bone biopsy specimens, remodeling activity was virtually absent at month 36. There was no evidence of a mineralization defect with denosumab-treated subjects. In the patients previously treated with alendronate, bone resorption parameters were further suppressed with denosumab therapy when compared with continued alendronate therapy.

The absence of tetracycline label may be an indication of very low bone remodeling and possibly even over suppression of bone turnover. As previously discussed by Dr. Popat, a large number of subjects in

Trial 216 had suppression of bone resorption marker CTX to the point where levels were undetectable. In order to further evaluate whether the lack of tetracycline label seen in the bone biopsy samples could be related to suppression of bone turnover seen with CTX levels, we questioned whether those subjects with no trabecular label also had undetectable levels of CTX at the month 1 time point.

This table shows that the biopsy samples from Trial 216 that had no label or double tetracycline present and whether these patients had undetectable levels of CTX or detectable levels of CTX.

As outlined, in patients with biopsy samples that had no detectable tetracycline label, month 1 CTX levels were also undetectable in 87 percent of denosumab-treated subjects at month 24 and 75 percent of subjects treated with denosumab at month 36; while patients with biopsy samples that had double label present, 100 of placebo subjects in both time points also had detectable levels of CTX and 67 percent of denosumab subjects had detectable levels of CTX.

As previously discussed, bone formation and bone resorption are tightly couple processes. With regard to the bone formation market P1NP, seven subjects who had bone biopsies had P1NP levels that were undetectable at month 12. That was the earliest time point P1NP was evaluated. All of those subjects were treated with denosumab, and six of those subjects had no tetracycline labeling on their bone biopsy specimens.

So in summary, based on the bone histomorphometry analysis, treatment with denosumab decreases bone resorption as evidenced by the suppression of bone histomorphometry parameters. Bone resorption and bone formation are tightly coupled processes, and treatment with denosumab also decreases bone formation or overall bone turnover.

One of the reasons we are concerned over the over suppression of bone turnover is the 2004 paper by Odvina, et al., that presented nine patients who sustained non-spine fractures while on bisphosphonate therapy. Some also had delayed or absent fracture healing. Bone histomorphometry from biopsy specimens

revealed absence of double tetracycline labeling as well as absent or reduced single tetracycline labeling in all patients.

So to summarize, the denosumab safety evaluation, overall when evaluating the denosumab safety database, the number of deaths was not higher with denosumab therapy. There was an imbalance in serious adverse events with denosumab use primarily by cardiac, musculoskeletal disorders and infections.

The adverse events of greatest concern are infections, new malignancies in the postmenopausal osteoporosis population, tumor progression in the breast and prostate cancer hormone ablation population and the dermatologic adverse events.

Data from the histomorphometry evaluation suggests that CTX -- from the evaluation of both CTX and histomorphometry suggest a possible over suppression of bone turnover. However, the long-term consequences of these findings are not clear.

To begin the summary of the risk benefit assessment of denosumab, I want to first present what the agency's interpretation of the populations of

patients that these indications are intended for. For the treatment of postmenopausal osteoporosis, the indication encompasses all patients who osteoporosis diagnosed by BMD or a history of a low trauma fracture. While we have not included the FRAX calculator as an inclusion criteria in the design of Phase 3 osteoporosis trials, we do believe that the treatment of postmenopausal osteoporosis indication also encompasses patients who are at increased risk for fracture based on the FRAX calculator.

The prevention of postmenopausal osteoporosis indication would include patients with low bone mass who are not considered at increased risk for fracture based on the FRAX calculator. The treatment of bone loss in patients undergoing hormone ablation for breast or prostate cancer, the indication would include patients who have evidence of osteoporosis diagnosed by the same criteria used for treatment of postmenopausal osteoporosis as well as those who have been on hormone ablation therapy and are demonstrating significant bone loss.

The prevention of bone loss in patients

undergoing hormone ablation for breast or prostate cancer, the indication will include patients with normal bone mineral density or low bone mineral density who do not have a significant bone loss with hormone ablation therapy or have newly begun hormone ablation therapy.

As shown in this slide, the agency's interpretation aligns with the currently published treatment guidelines for postmenopausal osteoporosis as previously reviewed by Dr. Siris. The National Osteoporosis Foundation recommends BMD testing for women over the age of 50 and initiation of therapy for those with a history of fracture, a BMD T score less than minus 2.5 or an increased ten-year fracture risk based on FRAX.

In the breast cancer population, the American Society of Clinical Oncology currently recommends BMD testing for all women on aromatase inhibitors and initiation of therapy for those with a T score of less than minus 2.5. For patients with low bone mass, yearly monitoring of BMD is recommended.

In the prostate cancer population, there are

no guidelines from major organizations. However, several reviews in working groups are available in the literature, including one from the North American Symposium published in Cancer in 2004. They recommend guidelines similar to those for breast cancer on aromatase inhibitor.

So in summary, denosumab is effective in reducing the incidence of fractures in postmenopausal osteoporotic population. Denosumab is also effective in increasing bone mineral density in postmenopausal women with low bone mass, in women undergoing aromatase inhibitor therapy for breast cancer, and in men undergoing androgen deprivation therapy for prostate cancer.

Neither of the primary trials evaluating denosumab in the hormone ablation population contained pre-specified plans to identify detrimental effects on cancer outcomes such as progression free survival or overall survival. Overall survival was an exploratory endpoint in both the breast and prostate cancer bone loss trials. However, given the eligible population for enrollment included subjects with non-metastatic

disease, few events would be anticipated.

In both the breast cancer hormone ablation trial and the prostate cancer hormone ablation trial, an insufficient number of events occurred and it is not possible to make any definitive statements regarding overall survival.

Safety concerns remain. These include the imbalance of infections; serious adverse events; most notably of the skin, ear and urinary tract; imbalance of endocarditis. While the event rates are low, they do exceed the background rate expected. The imbalance of infective arthritis, the imbalance of new malignancies in the postmenopausal osteoporosis population, the imbalance of tumor metastases in the cancer bone loss trial population, and the imbalance of dermatologic adverse events, most notably dermatitis events that were statistically significantly higher in those receiving denosumab.

One remaining question is whether denosumab reduces bone resorption and bone formation to the point that we need to be concerned regarding over suppression of bone turnover. In the denosumab

program, we have discussed the evidence of significant suppression of the bone resorption marker CTX. The bone formation market P1NP follows CTX and is also significantly suppressed.

When we combine this evidence with the bone histomorphometry findings, the concern remains the potential for long-term consequences of this degree of suppression of bone resorption and bone formation. Unfortunately, the state of the science for both markers of bone turnover and bone histomorphometry are such that it is not possible to predict long-term outcomes based on the data that we have. We can only say that they are unclear.

Another finding that may offer some suggestion of a potential for long-term consequences would be the hip fracture findings in year 3 of Study 216. The incidence of hip fractures increased compared to year 2 and was the same as placebo.

We welcome the committee's discussion on these findings as well as our consideration of our questions later this afternoon. And in closing, I would like to take the opportunity to acknowledge all

the members of the FDA review team who worked on this application and I apologize to anybody that I've inadvertently left off the slide. Thank you.

DR. CARSON: Thank you, members of the FDA staff for highlighting these points that you brought up.

We'll have now questions from the panel to all the presenters this morning. There is a lot of information we received on requests for four different applications on a variety of populations. I thought about how we could organize questions and then decided there was really no way to. So let me ask, though, just in the convenience, Dr. Eisenberg, if maybe you want to take the -- in bringing up anyone who you think most will be able to answer questions and then you can call from your group.

DR. EISENBERG: Sure.

DR. CARSON: So let me open it to the committee.

Yes, Dr. Mortimer.

DR. MORTIMER: I wonder if you could summarize the characteristics of the breast cancer

population for the 20 in the postmenopausal osteoporosis studies, the 20 compared to the 10. I mean, were there characteristics in age? Were older women more likely to develop --

DR. EISENBERG: Let me understand the question. When you say the cases of breast cancer that occurred?

DR. MORTIMER: Correct.

DR. EISENBERG: Okay.

DR. MORTIMER: What was the phenotype of the disease and what were the risk factors of the patients?

DR. EISENBERG: Sure. I think Dr. Roger Dansey, who was responsible for those programs, would be best able to respond to that.

DR. DANSEY: Good morning. As you saw in the initial presentation, just perhaps to orient you to how we evaluated breast cancer in the 216 study, what you're looking at is the overall population of women who developed breast cancer on studies, on the left part of the slide are the new diagnoses. And you can see there are 26 subjects on placebo, 28 on

denosumab. And for those subjects with a prior history of breast cancer, we have two on placebo and six on denosumab.

And in terms of the disease characteristics, which I think what you were asking, if we look at the stage distribution, for example, in the newly diagnosed, it's 16 Stage 0, 1 or 2 in placebo, 19 with denosumab. For the Stage 3 or 4, it's 4 and 5 unknown, 6 and 4 no status as you can see, 10 known positive, 9 known positive with denosumab and so on.

Histologically, there were three in situ cancers -- I'm sorry; three in situ cancers on denosumab, and the invasive groups were balanced.

We also did look at age. And there were no specific characteristics that I think we could identify clinically that would suggest any difference. And as I've pointed out, the numbers are similar.

DR. MORTIMER: Do you have a slide of the 20 and 10 from the PMO trials?

DR. EISENBERG: The 20 and 10 refer to discontinuations and they're distributed. I think Dr. Dansey can provide some background, but there's no

apparent relationship between discontinuation that Dr. Stehman-Breen commented in those studies and any of the background features. It appears simply to be a difference in whether they were in denosumab or placebo. There's no difference in the patients. I don't know.

Dr. Dansey, do you want to comment further? We did a pretty thorough analysis. It's simply discontinuation. These are all the cancers in that study.

Now, in the HALT study, did you want information on that one as well? There were new cancers in the HALT study. But Dr. Dansey can comment on that, in the breast cancer HALT experience, if you want to make comments.

DR. DANSEY: So perhaps just to reiterate what you said about the discontinuations. There was no protocol specified requirement for discontinuation. So local factors, which we assume are multifactorial, access to care and so on, likely would have applied. From the breast cancer point of view, the progression of disease, which was mentioned earlier, we've also

performed a very careful review of that information in the breast cancer HALT patient population.

And we see in the treatment period, three subjects on placebo with clear evidence of metastatic disease, four subjects on denosumab with clear evidence of metastatic disease. And so the treatment period of two years, you can see there -- and this is based on review of verbatim terms. And when we look at the off treatment phase, which is now subjects in follow up, we see two subjects with clear evidence of disease progression and two subjects on placebo.

And I would point out the 120 day -- the follow-up period is about to complete, and we'll have full data for that in the near future.

DR. EISENBERG: Two-year follow-up data.

DR. DANSEY: Two-year follow-up.

DR. CARSON: Dr. Emerson?

DR. EMERSON: I guess I have a question going back to the very beginning where Dr. Siris was talking about the impact and was talking about what populations should be treated. So particularly slides 10 and 12 was what I'm interested in.

DR. EISENBERG: Dr. Siris is working her way over the microphone and is probably best able to respond.

DR. SIRIS: It would be awkward if I fell and broke something trying to get to the microphone.

Could we have those slides up, please?

DR. EMERSON: So you're talking about the number of women with fractures versus the proportions of women within those groups.

Have you looked at the number needed to treat? I mean the concept that even though there's the large number of fractures among the negative 1.5 to negative 2.0 to sort of look at the extreme value, that with only 15 fractures per 1,000 person years, how many subjects would you need to treat to prevent one there as opposed to the right-hand side of that?

DR. SIRIS: That was not a purpose of the NORA study. The NORA study was not trying to tell anybody when to treat. The NORA study was able to show, because we had this very large population, that while the rates of fracture were highest in those with the lowest BMDs at baseline, which is what you would

predict from what the T score tells you, if you were to ignore the women with osteopenic T scores, you would miss about 52 percent of the women who actually fractured.

The take-home message there was we have to be able to risk stratify women with osteopenia in order to identify those osteopenic women at higher risk and those osteopenic women at lower risk. And one of the important risk factors in conjunction with osteopenia, for example, would be age. So an older osteopenic woman who's presumably had many more years to lose bone may have the same bone density as a younger osteopenic woman but the older woman's bone quality may be much worse. And by virtue of her age, she may have co-morbidities to make her more likely to fall, et cetera.

And the FRAX algorithm allows you to look at a series of risk factors in conjunction with the osteopenic T score to identify the higher risk patient in whom treatment would be appropriate and to identify the lower risk osteopenic whom you would not recommend for treatment.

DR. EMERSON: So then that leads to slide 12, which is the FRAX algorithm.

DR. SIRIS: Slide 12 was an example of the use of the algorithm in a patient who is 67 years of age, has a T score of minus 2.1 at the femoral neck. And this would define her as being osteopenic. When you analyze your risk factor profile, you see the list of risk factors under FRAX include -- yes.

DR. EMERSON: So one of the ones that I'd like to focus on in particular on this -- because we're going to a 10-year predictive range.

DR. SIRIS: Yes.

DR. EMERSON: And whenever you get into that game, if you take a newborn baby boy and predict risk of prostate cancer over 80 years, it's exceedingly high but we would not want to start preventive therapy or treatment at that age.

So we've got a 10-year predictive value and we've also got such risk factors as para fractured hip, so that's clearly just a sort of baseline risk factor, a family history and things like this.

What's known about the three-year history

that we've actually tested in this trial? What's that risk and how that relates?

DR. SIRIS: Well, FRAX gives you a 10-year risk which is the way FRAX was set up. The risk factors in FRAX were chosen because they are largely independent of bone mineral density, not 100 percent independent, but many of them are significantly independent of bone mineral density. They're showing --

DR. EMERSON: But my question here is, is this predicting people who will eventually develop disease or is this predicting people who have some clinical disease that will be rapidly progressive. And by the time we're looking at --

DR. SIRIS: I don't think it tells you any of those things. I don't think it works that way in osteoporosis. I think the concept that osteopenia is a precursor to osteoporosis is a somewhat outmoded concept. I think the point is that women after menopause lose bone. Women after menopause have a variety of risk factors that they may or may not have and that we now have a better of way of identifying

those patients at high risk for fracture than simply looking at a BMD, which is the way we did it since about 1994. And those individuals -- could I have the next slide up, please?

DR. EMERSON: Just to clarify. One of the big question is we've got two different indications. One is treatment.

DR. SIRIS: Yes.

DR. EMERSON: And we have 8,000 women treated under that. The other is prevention, and we have 300 women treated under that. And the concept of as we're looking for this, it will be very much concern to say how early should we start treatment. And looking at something like FRAX and looking at the risk factors, it''s certainly of a time range that we might worry that it's not necessary to start prevention yet.

DR. SIRIS: I think that's really an excellent question, and I think that the point is that, traditionally, prevention has been the prevention of bone loss. Treatment has been treatment of the disease in which fracture risk is elevated and,

therefore, you want to intervene to lower the risk of fractures. And I believe that's a throwback to the estrogen era when we knew that estrogen prevented bone loss and that women with estrogen appeared to have fewer fractures than women not getting estrogen. But that's an older concept.

It became clear -- and I think the NORA data was one of many studies that have documented this, that osteopenia is a risk factor. It's not a disease. It's a lowness of bone mineral density which in association with other risk factors can promote a fracture risk as high as simply having a T score of minus 2.5 depending on this combination. And the FRAX algorithm allows you to identify those people.

Now, it was interesting to hear what you said, Dr. Kehoe, that you consider a high FRAX score a treatment indication, which I would interpret as saying that if someone were osteopenic and their FRAX showed that they were at very high risk for fracture because of the other risk factors, that they would qualify for treatment under the treatment indication. Right now, third-party payers will not cover an

osteopenic woman because that's the only diagnosis you can give is osteopenia. A FRAX score is not a diagnostic category.

So we're going to be caught in a situation where we're going to have to redefine some things in order to assure that women, in fact, can get medication if it's deemed appropriate and also that it can be reimbursed. That's kind of an aside.

DR. CARSON: Excuse me. I'm sorry. We have a number of questions ready. And we do have time set for discussion, and I'd like to just limit this to questions about the presentations rather than discussion.

DR. SIRIS: Thank you.

DR. CARSON: Dr. Buzdar?

DR. BUZDAR: I have two questions. One was that it was brought up that these drugs, that this antibody can be given safely to patients who have abnormal renal function. But I did not see, maybe I missed it, what fraction of patient population in these study had abnormal renal function and was it changed or did it remain stable?

The other question which I have is about breast cancer, that there was 10 versus 20 new breast cancer diagnosed in the placebo versus the treatment.

In the patient population, did they estimate by using some of the models like Gail model or things like that, like what was the predictive probability of developing new breast cancer in the time frame which the patients were observed.

Is it above it, is it below it, or is it within the same range?

DR. EISENBERG: First, just to clarify your second question, then I'll ask Dr. Stehman-Breen. I think we responded to this -- to Dr. Mortimer's question.

There were 10 versus 20 refers to discontinuations in the clinical trial. The data we showed were actually 26 and 28 new breast cancers between denosumab and placebo. So that's the data in terms of new breast cancers in the trial. And I'll ask Dr. Stehman-Breen to comment on --

Dr. Mortimer, is it okay?

We'll finish the first question then.

So there were additional studies that were done in at-risk populations in terms of renal failure, and I'll ask Dr. Stehman-Breen just to comment on that briefly.

DR. STEHMAN-BREEN: So as I mentioned in my presentation, we didn't exclude women in the fracture study based on level of renal function, and about half the women had estimated glomerular filtration rates that were below 50 percent. So we actually had quite a bit of data with regard to the safety and efficacy in that population. The efficacy is identical to that seen in the larger population in those with various levels with renal function, and I'm happy to show you to that if you're interested.

In addition, you asked about whether there was any evidence of progression of renal disease. Denosumab is not renally cleared, and so it doesn't cause acute renal failure like bisphosphonates can. There was no evidence of differences in renal function. That was true with denosumab versus placebo in either our large PMO fracture study or a smaller dedicated study in renal dysfunction.

DR. EISENBERG: Any predictive factors in the clinical trial in the women who did have breast cancer? I don't think we saw anything that was predictive.

DR. BREHMAN-STEEN: No.

So perhaps we should go ahead and repeat the second question with regard to breast cancer so everybody can refresh their --

DR. BUZBAR: The second question was that you have two large subgroups treated with placebo and treated with your antibody. The question is that you can use a Gail model or some similar model to see that in the study period what will be the predictive probability of developing breast cancer in that period. Was that number above or below the threshold which it would --

DR. BREHMAN-STEEN: So let me first again clarify and perhaps if we can bring the slide up with regard to breast cancer from the core deck. We had a similar rate of new breast cancers diagnosed in our large PMO treatment study. What was different between the groups -- as you can see there were 26 in the

placebo group and 28 in the denosumab group. So that's a very important point.

What was different was the number of discontinuations due to adverse events of breast cancer, 20 in the denosumab group, 10 in the placebo group. And again, as we presented in the presentation, when we looked at these various prognostic indicators that you can see on the slide, there didn't appear to be a difference between those treated with denosumab or those treated with placebo that would differentiate the phenotype for the breast cancers.

I think Dr. Mortimer, you have a question.

DR. CARSON: Yes, but she's in line.

DR. EISENBERG: Just to complete the answer, if one looks at predictive rates, just at the background rate in this population based on standardized incident ratios for what we've observed, in this trial it would be .7 percent. It would be .7 versus the predicted rate. So it would be lower overall.

DR. CARSON: Does that answer your question?

Okay.

Dr. Johnson?

DR. JOHNSON: Yes, I'd like to start off by thanking all the speakers. The presentations were excellent and very useful in adding to our knowledge about this medication.

My main question is related to the possibility of immunosuppression. I know that you stated that you're continuing the seven-year expansion of the PMO trial and also four- and two-year extensions of the HALT trials.

Can you give us any further information, particularly related to risk of infection? Because that appeared to be a fairly consistent finding also in terms of dermatologic abnormalities. So do you have any data from any of the extensions that you can enlighten us on the risks of immunosuppression?

DR. EISENBERG: Dr. Stehman-Breen will comment.

DR. STEHMAN-BREEN: Yes, as you mentioned, the PMO fracture study has a large extension study that's ongoing. The study has been ongoing for a

little over a year. And as I mentioned, it's open-label, single-arm study. So we don't have a comparison group. But in the limited amount of data that we've been able to observe to date, we haven't seen any unexpected infections such as an unexpected higher rate of opportunistic infections.

Did that answer your question?

DR. JOHNSON: I know that, though, with the original study you didn't see an increase in opportunistic increase infections, but you saw an overall increased risk of infections.

Have you looked at that compared to the original study in terms of the risk?

DR. STEHMAN-BREEN: Again, we have relatively limited data to date, but we haven't observed a higher risk of serious adverse events of infection in the extension study to date. But we'll be, of course, to continuing to monitor to this as more of this data becomes available.

DR. CARSON: Dr. Margolis?

DR. MARGOLIS: Thank you. I have two somewhat unrelated questions, although one's directly

to the question that was just brought up.

There were many speakers who spoke about the increased risk of skin infections, serious adverse events, and they were listed as three different categories but just lumping them for a second. One of the speakers also mentioned that it could be because of local skin increased inflammation, and one also implied that there may have been only the lower extremity and could be related to venous disease.

So I was just wondering if you could talk a little bit more about these. Did they receive IV antibiotics? Did they have increased white counts, fevers? Were they recurrent? Were they related, much higher in people with venous disease? That was the first question.

Then the second had to do with the secondary analysis done by the FDA on Study 216 looking at hip fractures and claiming that by the third year the risk was about the same in the two groups. I guess my question is for those individuals who had hip fractures, were they maintained in the study or were actually the risks of the population, did that change

over time? And what is the likelihood of somebody having a second hip fracture if, in fact, those people were to maintain in this study? Thank you.

DR. STEHMAN-BREEN: So let me first address your question with regard to infection. It is a nodal finding that we saw an overall balance of skin infections adverse events but there is a higher risk of serious adverse events in skin infection.

Now, with regard to the characteristics, this illustrates across the program some important characteristics of the patients that developed cellulitis or erysipelas, serious adverse events of cellulitis and erysipelas. You can see the mean age was 79 in the placebo group and 74 on the denosumab group. The number of days from the last dose of study drug was similar between the two groups. The level of severity was generally similar between those in the placebo group and those in the denosumab group. Of note, there was one fatal adverse event of cellulitis in a subject who was quite complicated and had a very advanced pancreatic cancer that had invaded into the ventricle.

You can see that the vast majority of these were lower extremity infection, 100 percent in the placebo group, 88 in the denosumab group. And again, about half of them had risk factors for skin infections. Most as would be expected because they were hospitalized received IV antibiotics. But none of them discontinued due to the serious adverse event. And it's notable that there was only one occurrence in each group despite in the denosumab group continued exposure to denosumab.

DR. CARSON: Dr. Rosen?

DR. ROSEN: (Off mic)

DR. STEHMAN-BREEN: They had very typical courses. Not all of them actually had fevers and chills. The majority of them actually had -- about 15 percent had fevers. About half had pain. Half had swelling and erythema. About a third had warmth and about 15 percent had regional adenopathies. So for those of the panel that have taken care of these patients, they're often complicated and the diagnosis can be complex, I think as reflected by these clinical characteristics.

Did you want me to answer the second question?

DR. CARSON: I'm sorry. Go ahead, yes.

DR. STEHMAN-BREEN: So with regard to the finding where in the third year the incidence of hip fracture, although they were very small numbers, was slightly greater in those subjects that were treated with denosumab, I think one thing that's important to note is that the fracture rate in the placebo group, hip fracture, was actually declining in that last year, whereas in the denosumab group it was staying the same. There was no time by treatment interaction. And it's possible, as you're alluding to, that this may reflect a survivorship phenomenon.

You asked the question did subjects continue in the study after they'd had a hip fracture. They were, of course, invited to continue participation in the study. Many of them did continue in the study. There were some that at that point discontinued participation. But we did have subjects that were enrolled in the study were invited to continue the study even if they had been removed from

investigational product. And so we did make every effort to follow the subjects for as long as possible.

DR. CARSON: Dr. Rosen?

DR. ROSEN: Thank you. I have two lines of questions. The first relates to the discontinuation of denosumab in the two-year follow-up data. So can you give an estimate of the relationship between the change in BMD that occurs with denosumab over the first year after cessation of treatment, which is about 6 and a half percent, it comes down to zero, and its relationship to what happens with estrogen withdrawal?

Is it the same slope of change or is it more rapid? And if it is, how does that relate to the increase in fracture number that we saw in the individuals that were discontinued? There were nine in the denosumab and five in the placebo group in the 132 study.

DR. STEHMAN-BREEN: Let me first start by answering the second part of your question and then we have some data available that shows changes in bone markers in relationship to estrogen therapy.

With regard to your second question about fracture rates, as you noted, there were more fractures in those subjects treated with denosumab during that off treatment period. However, when we looked at osteoporosis or osteoporotic fractures, the rates were similar with four nonvertebral osteoporotic fractures in the denosumab group and four in the treatment group.

Now, we have done a post hoc analysis subsequent to completion of the briefing document where we've looked at those subjects in the PMO fracture study that discontinued therapy over the course of the study but continued participating in the study. When we looked at those fracture rates, we included in this analysis subjects that had had at least seven months of follow-ups since their last dose of investigational product. And what you can see are the fracture rates per hundred years were similar between those treated with placebo and those treated with denosumab. Again, recognizing that it's not the perfect analysis, but it does give us some sense of fracture rates after discontinuation.

DR. ROSEN: But if I'm not mistaken, in the HALT breast cancer study, there was twice as much fractures, all fractures, after discontinuation of denosumab as well.

DR. STEHMAN-BREEN: Yes, you are correct that were more fractures in the discontinuation period. It's in the breast cancer study. It's important to keep in mind two things, one, these subjects, many of them continued on the aromatase inhibitors and had significant reductions in bone mineral density during that follow-up period. And when we looked carefully at the concomitant medications in those two populations, you can see in this figure that subjects in the placebo group were treated with alternative therapies, bisphosphonates typically, twice as frequently as those subjects treated with denosumab, making the analysis quite confounded.

In addition, in that study, all fractures were captured through adverse event reporting. And unlike our other study, with our study, the PMO prevention study, were not confirmed by a central

review.

DR. ROSEN: Just to follow up, though, the rate of change of 6.5 percent in the first year of loss, how does that relate to estrogen withdrawal and the turnover markers which go up considerably during the first year?

DR. STEHMAN-BREEN: Thank you. I'm going to have Dr. Javier San Martin, who was responsible for the conduct of this clinical trial, comment on that finding.

DR. SAN MARTIN: This is the study looking at discontinuation of HRT published a few years ago by Dr. Gallagher. And as you can see, the decrease in bone mineral density is similar to the one we see with denosumab discontinuation. In the upper panel, you see the lumbar spine bone mineral density and in the lower panel, you see the total hip. So both the increases in bone turnover and also the decrease in bone mineral density are relatively similar. And a similar finding was also seen with risendronate. So this --

DR. ROSEN: But Dr. Siris' part of the study

that looked at the post-estrogen follow-up in NORA and their rate of hip fractures were increased. So how do you balance that rapid change with the possibility that there could be an increased risk of fracture?

DR. SAN MARTIN: Yes, that was a finding in the NORA study. Also, for the numbers that were fractured, there was not an increased risk. And I think the more relevant study to look at this data is the WHI discontinuation. And in this study, which is a very large study that really in a more controlled fashion followed patients that discontinued hormone replacement therapy, there was no difference in hip fracture incidence.

DR. ROSEN: Right, except most of those women were not osteoporotic, correct?

DR. SAN MARTIN: That's true. The same applies for the NORA study.

DR. CARSON: Did you get your questions answered?

DR. ROSEN: Yes, thanks.

DR. CARSON: Dr. Bennett?

DR. BENNETT: I have three questions that

relate to skin infections. I'm more interested in the mechanism than I am concerned about the safety implications because these are easy to detect. There are complications of these. And particularly in the United States where so many of the elderly have replaced joints, you can have skin organisms, usually staphylococcal species infecting an existing prosthetic joint. Very few of the patients in this study were from the US, so I don’t know how many prosthetic joints were in the elderly in this study.

But the other issue that will frame the last question, the third question that I have, is that the elderly are prone to skin infections at the lower extremities because of loss of skin elasticity as well as the frequent occurrence of dependent edema. So my three questions are first, with the endocarditis or joint infections due to skin organisms, in the handout the only one I found was an endocarditis turning staph aureus. I wondered if you knew about that. The other, I was surprised with the incidence of arthritis and I wondered how many of those were in prosthetic joints.

The last question is, is there a reason to think that the denosumab might have influence collagen deposition? Because if it did that, it might have a subtle or prolonged effect on skin elasticity, which could then explain increased incidence of infection in the lower extremities.

DR. EISENBERG: I think with regards to the third question, our preclinical data would not suggest there'd be an effect on collagen. The other two questions, we do have some information on. Again, Dr. Stehman-Breen looked at each of these, both the infective arthritis and the endocarditis, so I'll ask her to comment.

DR. STEHMAN-BREEN: So with regard to the infective arthritis cases, as you heard in the presentation, there were eight in the denosumab group in the fracture study, and there were none in the placebo group. But when we looked at these adverse events, none of them were serious adverse events. None of them required intravenous antibiotics, and none appeared to be a classic septic joint. And none of them had evidence of a joint replacement. And it

appeared, as we looked carefully at these cases and the way that these verbatim terms are reported, that if you report an infection at the knee, it maps to an infective arthritis. And therefore, it appeared that these were likely exacerbations of arthritis or in some cases cellulitis.

DR. BENNETT: That's clear. Thank you.

DR. EISENBERG: I'm happy to comment on the endocarditis. Some cardiologists offered to bring the slide up.

If we looked overall in our clinical experience and recognizing the citation to cases of endocarditis in the New England Journal, which looked at very careful case criteria, first of all, we did have additional cases in the placebo patients. So for the overall population, the difference is small. I reviewed all of these cases. Typically, one case clearly required a valve replacement, and so there clearly was documentation of endocarditis.

In the other cases, the cause of the pathogen was not defined, and it's a typical echocardiographic diagnosis of vegetations on the

valve. So we have one case clearly where we were certain that it's endocarditis.

My recollection of those cases was that these were incidental findings during these patients' hospitalizations so that a causative -- going back to the concern around skin, I don't believe we have any evidence that that would have been the case.

DR. BENNETT: Thank you.

DR. CARSON: Dr. Mortimer, back to you.

DR. MORTIMER: I'm sorry and I'm really not perseverating on this point, but the clarification about the breast cancer incidence. Because the fact is twice as many women went off study because of a diagnosis of breast cancer. Therefore, the drug was stopped. So ultimately, with stopping the drug, the incidence in breast cancers turned out to be equivalent. And I guess my concern in looking at that is does this drug somehow shorten the length time? Is there a length time bias? Does it sort of make these cancers more apparent earlier than they would have?

So is there a difference in how these cancers were diagnosed? I mean, were the treatment

more hypervigilant than the placebo group?

DR. EISENBERG: Sure, and that's a good question. And, of course, there is also the confounding in general that we had slightly more cancer deaths than in the placebo group that also censure some subjects. But perhaps Dr. Stehman-Breen can comment on the discontinuation.

DR. STEHMAN-BREEN: So there didn't appear to be any pattern that would suggest that these subjects were diagnosed earlier. You can see that we have timing of the breast cancer event, and you can see month 1 to year 1, year 1 to year 2, year 2 to year 3, they're relatively well balanced. It didn't appear that there was anymore rapid diagnosis of the disease certainly in the denosumab group.

There are many reasons that people discontinue therapy, and they can vary from living very far from an investigative site to having a support system that's needed for other reasons. And after a very thorough review, we've really been left with the conclusion that this doesn't appear to be due to phenotypic differences in the cancer and really is

a chance finding. But I'm happy to answer additional questions.

DR. EISENBERG: I think just to answer your question, Dr. Mortimer, to make sure we're clear on this because there isn't more censuring of cases.

So if you look at this slide, you can see that, in fact, you have a pretty balanced time for discontinuation. So the yellow shows the patients who discontinued relative to the last slide. And again, it's eight versus nine. It really seems to be independent of any of the other findings. So that's the specific answer.

DR. CARSON: Go ahead.

DR. MORTIMER: But the fact is the incidence went down when you discontinued the drug. It equilibrated to the placebo.

DR. EISENBERG: I don't believe that's true.

DR. STEHMAN-BREEN: They had already been diagnosed at the time that they discontinued so they would count --

DR. MORTIMER: Right, so my question continues to be are they found earlier because of this

drug somehow making them grow and becoming morphic?

DR. STEHMAN-BREEN: There didn't appear to be any evidence of that. But let me ask Dr. Roger Dansey, who's our oncologist and who has been responsible for our oncology programs, to come to the microphone and perhaps we can provide an answer.

DR. DANSEY: So I think I can reiterate the points that have been made. The rates of new cancers are essentially the same on this study. The reasons for discontinuations are not apparent. The types of cancers, the clinical characteristics are similar. And I'm not sure that we necessarily connect the discontinuation rate because of the timing, as you saw, being scattered across those three years with necessarily some early effect of denosumab somehow bringing the cancer to the full -- in a quicker time period than on placebo arms.

DR. CARSON: Thank you.

Ms. Solonche?

MS. SOLONCHE: My first question is, can you provide any data on the percentage or numbers of clinical trial participants who suffered two or more

adverse events? While you think about that --

DR. EISENBERG: We could probably come back to you with that. I don't believe I have that readily available, but many subjects in terms of nonserious adverse events will report multiple adverse events. But I believe we can provide that to you perhaps after lunch. We'll see if we can give that information.

MS. SOLONCHE: Thank you.

The second question is, do you find that this monoclonal antibody has any effect on cancer antigen tests? For example, the CA-125 for ovarian cancer or any of the CEAs?

DR. EISENBERG: No, it's a very good question, but the antibody is very specific for human RANK ligand, so we wouldn't expect it to have any other binding activity.

MS. SOLONCHE: Okay. Thank you.

DR. CARSON: Dr. Richardson?

DR. RICHARDSON: Practices around the world certainly vary country to country and I think patients to patients, physicians to physicians. I was taken by one of the things that Dr. Stehman-Breen mentioned,

that most of the data on cataracts in I guess it was the prostate cancer trial were dependent on surgical reports. And it would seem to me that this must be a gross underestimate of the incidence of cataracts in this group.

DR. EISENBERG: This would have been new cataracts that were identified by the adverse event report of having the requirement for surgery. I think it's a fair point that without a properly conducted ophthalmologic study, I don't think we can say. If we bring up CTA, I think this sort of gives you a sense of how one would think about this in terms of background rights. And you're right. I mean clearly, a proper ophthalmologic examination identifies more subjects and it may be that you'd find something different than those who require surgery. So I think you're right about that, yes.

DR. RICHARDSON: Let me ask, make one other statement. Kind of woven throughout the applicant's materials and the FDA analyses, it seemed to me that there were instances in which there were important pieces of information that were lacking. Family

members not giving important pieces of information such as cause of death, which in these kinds of studies I think is extremely important, and it I think raises questions about the rigor with which some of this information was gathered. And I think these kinds of things really do, in fact, reflect on the integrity of the database as a whole.

We heard that only a small number of patients from US were entered. Can you tell us where these patients came from, where in the world and the kinds of practices that were recruited for this?

DR. EISENBERG: Absolutely. Dr. San Martin was involved in conducting the study, so I'll have him comment.

DR. SAN MARTIN: Thank you. Here we have the distribution of patients in the Study 216, which is the PMO study. As you can see, about 45 percent of patients came from Western Europe, 34 from Eastern Europe, 12 from Latin America, 7.4 North America, and 1.2 percent from Australia and New Zealand.

DR. CARSON: Question's answered, Dr. Richardson? Okay.

Dr. Collins?

DR. COLLINS: Yes, hi. I had questions about the hypocalcemia and the related mineral metabolism, the physiology related to that.

So given the very dramatic degree of suppression of bone turnover, I'm actually surprised that there wasn't more hypocalcemia and wondered about then what compensated for that. And it must be secondary hyperparathyroidism or elevations in parathyroid hormone and subsequent elevations in 125-D.

So one question would be then, do you have the data on the degree of secondary hyperparathyroidism and how prolonged that is, the data on 125-D levels? And related to that then, were cases of hypocalcemia more common in patients that were 125-D deficient? Were they more common in patients with renal insufficiency who couldn't mount a 125-D response?

DR. EISENBERG: We have some of the answers to that. Again, remember, of course, in the pivotal trials, everybody was supplemented as well with

calcium and Vitamin D, which certainly helps. But I think Dr. Stehman-Breen can answer some of the questions that you're getting at. We can't answer them all.

DR. STEHMAN-BREEN: With regard to your question about the compensatory mechanisms, you're correct. This slide illustrates the transient increases that are observed in PTH that are observed consistently across studies. And on the right side of the panel, you can see the reductions in serum calcium. And so they are well coupled with each other but are transient.

I think your second question was whether or not these levels of -- oh, you asked about Vitamin D. So we measured Vitamin D at baseline. We didn't do additional assessments of Vitamin D throughout the study. As Dr. Eisenberg pointed out, everybody was supplemented throughout the study. We did do assessments looking at whether reductions in calcium varied by whether or not someone's Vitamin D level was greater or less than 20, between 12 and 20, and there didn't appear to be a significant difference.

We looked carefully with regard to renal function. And generally, there was slightly greater reduction in serum calcium in those subjects. This is in our PMO fracture study. And those subjects with greater degrees of renal dysfunction but levels of calcium less than 7.5 were unusual. And as you can see, were also observed in the placebo group. So with regard to renal function, with supplementation of calcium and Vitamin D, it appears to compensate for inability to convert to active Vitamin D at very low levels of renal function.

DR. CARSON: Did you get your question answered?

DR. COLLINS: Yes, I did. And I guess so there clearly was development of secondary hyperparathyroidism, but it appeared to be relatively transient.

But I wondered, there seems to be some evidence of secondary hyperparathyroidism on some of the bone biopsy specimens, particularly the case of marrow fibrosis, the trabecularization of the bone marrow. And I wonder if this could be the effect of

chronic secondary hyperparathyroidism.

DR. STEHMAN-BREEN: So just to clarify, the marrow fibrosis was in a subject treated with alendronate. I'd like to ask Dr. --

DR. COLLINS: Alendronate alone or alendronate --

DR. STEHMAN-BREEN: Just alendronate.

I'd like perhaps to have Dr. Dempster come to the microphone and comment on your second question with regard to PTH and bone biopsies.

DR. DEMPSTER: Thank you very much. My name is David Dempster. I'm a professor of clinical pathology at Columbia University in New York. I wanted to specifically comment on the one biopsy and Dr. Collins' question.

The biopsy was taken long after -- this was a 36-month biopsy, so that would be long after any transient increase in PTH.

This is a void in the cortex that we see quite routinely in patients with osteoporosis. As seen here, it is described in the FDA document as resorption. However, if we go to a higher power

slide, you can see that the inner aspect of the void is lined by osteoid and osteoblasts. So this is a formation site at this point and clearly is filling in.

The sponsor went back and looked at micro CT images because of the concern raised. You can see this is a paired biopsy. One was taken at month 24, and one was taken at month 36. And it's month 36 where this anatomical variant was observed. Clearly, the month 36 biopsy is taken from a different anatomical site. You can see that it's substantially bigger.

Interestingly, while the void can be seen in one orientation, if it is rotated through 90 degrees, as you can see, the void disappears. So I think this tells us that this is a very localized porosity within the cortex. And furthermore, if you look at the lower image, again the right-hand image, which is a reconstructed micro CT image of this specimen, you can see that there is good connectivity between cancellous bone and cortical bone. So I think the implication that this would result in a significant loss of bone

strength is not true in this particular case.

DR. CARSON: Let me just say there are about four more questions in the queue and we'll go ahead and get as many of these answered until 12:15 and then break for lunch. And then those that are left over, we do have time for more questions this afternoon.

I do have a question. And that is, I noticed in the material that you've presented to us that the benefit of the drug with bone mineral density in Study 216 decreased compared to placebo as body weight increased. And because such a large percentage of the participants were not from the United States, and perhaps in countries where weight is not as much of a health problem, I wonder if you have more information on the weight of these subjects and how it affected outcome.

DR. EISENBERG: My understanding is -- and I'll ask Dr. San Martin to comment -- that there wasn't a relationship between body weight and efficacy. But perhaps Dr. San Martin can comment.

DR. SAN MARTIN: Thank you. This is a typical finding, which is that increase in bone

mineral density, bone mineral density on the baseline weight. So it is commonly observed that patients who have higher body mass in this -- or heaviest, they have baseline higher bone mineral density. And because their bone mineral density is present as percent change, you usually see less increase in terms of percent change in those patients who have higher BMI, or body mass index, or heaviest weight.

I don't know if we have a slide that specifically look at this, but a bar figure, a different baseline body weight.

DR. EISENBERG: Can you comment? I think Dr. Carson also was interested in the body weight distribution in the 216 trial?

DR. SAN MARTIN: Right. So the mean BMI was about 25, which is typically seen in osteoporosis patients. I don't really have data to compare that with the US population in general. I don't know if that answered your question.

DR. CARSON: I'm sorry. I remembered incorrectly. You state that the effects of the drug in preventing new vertebral fractures were rapid and

sustained statistically significant differences between the drug and placebo groups were observed. But the differences decreased with increasing body weight.

DR. SAN MARTIN: So I referred to bone mineral density, but we do have the data looking at vertebral fracture by weight.

Here you see the primary efficacy data as has been presented before which shows a 68 percent reduction in new vertebral fracture. And when you look at the different baseline body weight, you see that the risk reduction is very consistent, going from 72 percent to 65 percent in those patients with higher BMI or higher baseline weight.

DR. CARSON: Thank you.

Dr. Rosen?

DR. ROSEN: I'd like to explore the suppression in bone turnover and get a sense from the sponsor about their feeling about the absence of label in 36 percent of the month 36, and then explore with you a little further the relationship of the absence of detectable CTX to the absence of labels.

So could you start with a little discussion about your interpretation of the absence of any label?

DR. STEHMAN-BREEN: So as you're alluding to, there was absence of label in either the cortical or trabecular bone in approximately one-third of the subjects in which we conducted bone biopsies. This is consistent with the mechanism of action of denosumab and the level of suppression of bone turnover that we've seen with the serum marker CTX.

The clinical implications of that reduction in the amount of labeling in bone, we can comment on with regard to the three years of follow-up in our pivotal fracture study and those data you've heard. We've also not demonstrated any adverse impact of that level of bone turnover reduction as reflected by labeling in terms of atypical fractures or abnormalities in fracture healing, or abnormalities in healing of fractures.

We are committed to continuing to monitor this in our long-term safety program, as we recognize that the safety of the drug, the long-term safety, can only be defined by those sorts of programs. In

addition, we have bone biopsies that will be conducted as part of that long-term extension study to help us continue to understand what the bone histology and histomorphometry appears over long-term with long-term treatment of denosumab.

DR. ROSEN: Have you looked at the demographic characteristics of those individuals that have these suppressed -- the absence of the label and how that might relate either to the absence of detectable CTX in your subjects?

I mean, I think the issue here is, can we pick out those individuals that could be at particular risk for suppression, for marked suppression, in turnover, which then subsequently might put them at risk for atypical fractures down the road?

DR. STEHMAN-BREEN: There haven't been any variables that have been able to predict those subjects that are going to have a lack of label. And it's also again consistent with our mechanism of action. So although if we could potentially identify a risk factor for lack of label, it ultimately would be most relevant if we did find that there was an

adverse outcome associated with that level of suppression.

It's important to keep in mind that denosumab is reversible. And so unlike bisphosphonates, if we did see an adverse outcome, associated this with long-term treatment of denosumab, we do have the ability to discontinue the therapy with return of osteoclast function.

DR. ROSEN: So I understand that that's the mechanism of action, but we're not used to seeing the absence of label in a third of the subjects. And so I think we need some clarification about what the importance of that is. We're not making any judgments; we're just trying to understand or appreciate how that compares to bisphosphonates such as zoledronic acid where label was present in 81 out of 82 subjects. So can you give us some clarification on that?

DR. STEHMAN-BREEN: Yes, I understand your concern, and I think what I'll do is perhaps have Dr. Dempster come to the microphone and address your question.

DR. DEMPSTER: Thank you. As the panel is well aware, remodeling serves two main functions. One is metabolic, as Dr. Kehoe has mentioned, and the iliac crest and cancellous bone, specifically in the iliac crest, is considered to be a highly metabolically active site. The other function is mechanical repair. And at that particular site in the iliac crest, there is very little need for mechanical repair because it's not a weight-bearing site nor is it a fracture site. And, in fact, if you look for micro damage at the iliac crest, there are vanishingly small amounts of micro damage.

So the trigger for targeted remodeling and mechanically necessary remodeling is very low at that site. I therefore think it's reasonable to assume that we could see almost complete or indeed complete suppression of remodeling at that site without losing the necessary remodeling that is mechanically driven at other sites.

To support that, if I could have slide 49, this is an analysis similar to the one that Dr. Kehoe presented. But what I asked the sponsor to do was

look at the patients who had no label, and they're shown with the yellow label third from the left at both month 24 and month 36, and compare that, looking at serum CTX values, with patients who either had single or double label to the left of these lines or to the placebo group, to the right of the line with no label. And what you see is there's substantial overlap.

Clearly, this is later on in the treatment course. These CTX values were not taken at month 1. They were taken at the time of the biopsy. But I think what this tells us is that even if there's no label in the biopsy, in a substantial number of these people, there is still remodeling occurring at a substantial rate at other parts of the skeleton.

DR. CARSON: Go ahead, Dr. Rosen.

DR. ROSEN: I just want to follow up with one final informational question, and I'm not sure if Dr. Dempster can answer that. But the strength testing that you did, I understand the absence of rodent model, but relative to this, the strength testing you did was vertebral strength testing, did

you do repetitive cyclic testing to look for fatigue or was this purely vertebral testing?

DR. EISENBERG: Let me ask Paul Kostenuik who is responsible for the preclinical program in terms of bone studies.

DR. KOSTENUIK: Thank you for the question. We only performed monotonic testing, destructive compressive testing of the vertebrae and other sites.

DR. ROSEN: Sorry, Paul. Was that just the vertebrae?

DR. KOSTENUIK: We assessed whole vertebral bodies, and we also assessed trabecular cores from the vertebrae. And all of those analyses in three separate studies showed improvements in the structural properties of bone strength and no reductions in any of the material properties we measured.

DR. CARSON: Dr. Emerson, final question before lunch.

DR. EMERSON: This is a question about the diverticulitis that you did, and maybe I'm just parading how bad a student I was in medical school. But I thought diverticulitis was the infection and the

diverticulum was just an anatomic risk factor for having diverticulitis. So why would we be interested in including the diverticulum in there if, in fact, what this treatment might have done is increased the risk of diverticulitis among those with diverticula?

DR. EISENBERG: Sure, I'll have Dr. Stehman-Breen comment briefly about the aggregated cases. But part of this is, as we've highlighted, MEDRA is quite useful in terms of providing a means to code cases. You have to look at the individual clinical cases. I would say when you do that for diverticulitis, there's still some small differences. But we can provide some additional context.

DR. STEHMAN-BREEN: So you are correct in your recollection from medical school. But when we went back and looked carefully, as Dr. Eisenberg noted, there are some challenges in just looking at the preferred terms. And for the serious adverse events, we had very detailed case reports. We were able to look at all of the adverse events, including diverticulum serious adverse events that may be related to diverticulitis or may be diverticulitis.

And, in fact, we did have a total of two cases in the placebo group and two cases in the denosumab group that weren't coded as diverticulum. But when you read the cases, they actually indicated they were diverticulitis.

DR. CARSON: Dr. Emerson is clearly hungry, and Dr. Goozmer had a question. If we can save that, we'll start our afternoon session with that.

We'll break for lunch now. It will be served in the restaurant you can reach by going out the hall, turning left, and going through the lobby. And then we'll reconvene at 1:00 and start the open public session shortly thereafter.

Please take any personal belongings with you at this time. And committee members, please remember that there should be no discussion about the meeting during lunch with each other, with the press, or with any member of the audience. Thank you.

(Whereupon, at 12:160 p.m., a lunch recess was taken.)

A F T E R N O O N S E S S I O N

DR. CARSON: Welcome back. We'll begin the afternoon session with the public hearing.

Both the Food & Drug Administration and the public believe in a transparent process for information gathering and decision-making. To ensure such transparency, at the open public hearing session of the Advisory Committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the committee of any financial relationship that you may have with the sponsor, its product, and if known, its direct competitors. For example, this financial information may include the sponsor's payment of your travel, lodging or other expenses in connection with your attendance at the meeting.

Likewise, FDA encourages you at the beginning of your statement to advise the committee if you do not have any financial relationships. If you

choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking. The FDA and this committee place great importance in the open public hearing process. The insights and comments provided can help the agency and this committee in their consideration of the issues before them.

That said, in many instances and for many topics, there will be a variety of opinions. One of our goals today is for this open public hearing to be conducted in a fair and open way where every participant is listened to carefully and treated with dignity, courtesy and respect. Therefore, please speak only when recognized by the chair and thank you for your cooperation.

The first speaker is Kathleen Cody, the Executive Director of the Foundation for Osteoporosis Research and Education and the American Bone Health.

MS. CODY: Thank you. I have no disclosures about my travel to be here at this meeting today, but as a non-profit organization, I do receive financial support from most of the pharmaceutical companies and

other industry individuals and companies.

I'm here to represent the 44 million Americans who are affected by osteoporosis and low bone mass. Only a few of them know that I'm here today, and in fact, only a few of them -- most of them don't even know that they are at risk for osteoporosis.

So how can that be? This disease is going to touch the lives of so many people. In fact, many of the people in this room are going to be touched by osteoporosis in their lifetime. It might not be you, but it will be perhaps your grandmother or your mother or your sister or your father or perhaps even a friend.

Osteoporosis is terribly overlooked by both patients and by doctors. So how can that be? Is it the age of the patients that are affected by osteoporosis? Is it the fact that they're mostly women who are affected by osteoporosis? Or is it that people think it's normal to shrink several inches as they get older.

So how would you ever know if you had

osteoporosis since it's a silent disease? Well, you could be tested. A bone density test is more accurate in predicting fractures than blood pressure is of a stroke, or cholesterol is of a heart attack. A bone density test is pretty simple. It's not painful and right now, it doesn't cost very much. And yet only 13 percent of the women of Medicare age in 2008 were tested for osteoporosis.

So if you had a bone density test and found out that you were at moderate or high risk for having a fracture, wouldn't that give you some motivation to make some changes in your lifestyle and maybe get treated to avoid a fracture? So if people aren't tested, they find out they have osteoporosis when a bone breaks. Osteoporosis is the leading cause of fractures among older adults and it always results in bad outcomes: immobility, disability, and even death.

With this knowledge, wouldn't it surprise you that 78 percent of the individuals who have fractures are never evaluated for the underlying cause, which in many cases is osteoporosis and then treated to prevent more fractures?

We have lots of fractures that could be prevented. There were two million in 2005. In fact, today while we're at this Advisory Committee meeting, there will probably be about 1,500 fractures related to osteoporosis.

So if disability, pain, and even death don't worry you enough, perhaps knowing that fractures cost this country over $21 billion. That's $21 billion in 2007. And left unfettered and compounded by our aging population, the costs are expected to skyrocket to $25 billion by the year 2025.

So these are pretty dismal statistics that I'm sharing with you today and we're here together, I hope, to start to change them. We need as many tools and as many partners in this fight as we can get. There's a role for everyone and everyone has a role in making a difference here. So as a committee, you're here to determine whether this is an appropriate drug to use in this fight against osteoporosis.

I would like to thank you on behalf of all of the people who are risk for osteoporosis or have osteoporosis. I would like to thank Amgen for their

work over all these years in bringing us yet another tool as a possible solution to the treatment of osteoporosis. And I'd also like to thank the private donors of my organization who made it possible for me to be here today.

So Madam Chairman, if it's acceptable to you, I have a document that more deeply outlines the history of what's been done to date in the fight against osteoporosis, and also a book of photographs and stories of patients who've been affected by this disease I'd like to leave for the record.

DR. CARSON: Thank you. If you would just leave it for now with our transcriber.

Next is Roberta Biegel of the National Osteoporosis Foundation.

MS. BIEGEL: Good afternoon. I've received no financial assistance to be here today and I'm speaking on behalf of the National Osteoporosis Foundation, which accepts financial support from individual donors, foundations and corporations, including pharmaceutical companies in the form of educational grants.

The National Osteoporosis Foundation is appreciative of the opportunity to address the committee on the prevalence and burden of osteoporosis and the need for effective therapies for millions of Americans with and at risk for osteoporosis.

NOF is the nation's leading voluntary health organization solely dedicated to osteoporosis and bone health. It's mission is to prevent osteoporosis and related fractures, to promote lifelong bone health, to improve the lives of those affected by the disease and to find a cure thorough programs of awareness, advocacy, research and education. NOF is pleased to be a resource for the Food and Drug Administration.

As you've heard today, osteoporosis is a disease characterized by low bone mass, deterioration of bone tissue and architecture, compromised bone strength and an increase in the risk of fracture, especially the hips, spine and wrist, although any bone consequently can be affected. In simpler terms, osteoporosis weakens bones so that they break easily.

Osteoporosis is an intermediate outcome for fractures and is a risk factor for fracture, just as

hypertension is for stroke or high cholesterol is for heart attack. Fractures due to osteoporosis are common, costly, and often become a chronic burden on individuals and society.

Osteoporosis is often called a silent disease because bone loss often occurs without symptoms. People may not know that they have osteoporosis until their bones becomes so weak that a sudden strain, a bump or a sneeze, causes a fracture or a vertebrae to collapse. Collapsed vertebrae initially may be felt or seen in the form of severe back pain, loss of height, or spinal deformities such as a stooped posture.

Individuals with very severe osteoporosis may have difficulty breathing or even digesting their food, because their respiratory or digestive systems are so compressed that they are unable to function adequately. Osteoporosis may keep people from getting around easily and doing the tasks and activities that they enjoy and need to do on a daily basis.

This can cause people to feel isolated and depressed and sometimes can lead to other health

problems such as people being afraid to leave their home for fear of falling or they may not be able to shop for groceries and have adequate food and a balanced diet, or they may lack physical activity and they may not be able to meet with friends and socialize. These individuals often are invisible in our society and they often don't receive the medical care and support that they need.

There are multiple risk factors that increase the likelihood of developing osteoporosis and fractures. And as you've heard today, certain medicines and treatments for cancer might be a cause for osteoporosis.

NOF estimates that 44 million Americans have osteoporosis or are at risk for developing the disease because of low bone mass. That represents 55 percent of the population 50 years and older. And by 2020, the number of those with or at risk for the disease will increase to 61 million. A recent study estimates that by 2025, there will be three million fractures. Osteoporotic fractures also account for more than 4 million hospital admissions, about 2.5 million

physician visits and more than 180,000 nursing home admissions. A woman's risk of hip fracture is equal to her combined risk of breast, uterine and ovarian cancer.

NOF in concert with its partners at the National Coalition for Osteoporosis and Bone Diseases in 2008, convened a meeting of 150 stakeholders to develop a national action plan and agenda to advance bone health promotion and disease prevention. Meeting participants built on the findings and recommendations of the 2004 Surgeon General's Report on bone health and osteoporosis.

The discussions were the basis for a national action plan for bone health, recommending steps for advancing bone health across the United States and one of the priority areas is to improve diagnosis and treatment. NOF is pleased that as a result of the research performed during the last 15 years, patients and their physicians now have a choice of osteoporosis medications that can prevent and reduce the risk of the disease.

However, because of individual differences

there remains a continuing need for new, safe and effective osteoporosis medications. Although osteoporosis is most commonly diagnosed later in life, it's not an inevitable consequence of aging. It's a disease that's largely preventable and treatable. Individual differences should be considered by healthcare professionals to determine what they can do to prevent or treat osteoporosis.

A bedridden person in a nursing home who takes multiple medicines clearly can be viewed differently from the person who is physically active and does not suffer from other ailments. Although many individuals remain undiagnosed and untreated, and you just heard fewer than 15 percent of women, Medicare beneficiaries, eligible for osteoporosis testing, take advantage of this benefit.

Those who are diagnosed and treated, often do not adhere to treatment. Unlike with some other diseases, a patient initially and for a long time may have no indication that their medication is working and that their bones are getting stronger. Their improved bone mass and reduced fracture risks are not

readily apparent and need time to develop. Usually they will not have a bone density test for two years. Sometimes after one year, if the physician thinks it's appropriate. Without obvious feedback, many patients lose motivation to continue with their osteoporosis medication.

The burden of medication for older people and post-menopausal women specifically can be very substantial. People agree that sub-optimal compliance with osteoporosis medications persistently decreases over time. Unfortunately, the long-term consequences of not complying is decreased bone density and sometimes worse.

In conclusion, the incidence of osteoporosis is estimated to increase and according to the surgeon general, the consequences of poor bone loss are disability, diminished function and loss of independence or premature death. Because of the complexity of osteoporosis and lack of adherence to treatments, NOF believes there's a critical need for a broad array of medications to prevent and treat the disease. With a wide range of approved, safe and

effective medications for the prevention and treatment of osteoporosis, physicians and patients may agree on an individualized approach to improving a patient's bone health. Thank you.

DR. CARSON: Thank you.

Marilyn Brown?

MS. BROWN: I live in Silver Spring, Maryland; travel to Bethesda, Maryland for my treatment and they pay for my parking. I was diagnosed with osteoporosis in my mid-sixties. I was put on Fosamax which permanently damaged my esophagus causing daily heartburn and I still take medicine daily for that. I was referred to Dr. Michael Bolognese. My current study is denosumab and this is my second study.

My bone density has increased 15 percent in the last three years. I am 83 years old and a very active person. I play tennis two to four times a week, clean my own home, cultivate, plant and harvest the vegetable garden, pick our strawberries, raspberries and blueberry plants, prune 21 shrubs, a hedge, two plum trees and a peach tree.

I'm a retired microbiologist who worked in clinical micro at NIH, National Institutes of Health, for 21 years. And after donating blood to Chemistry Clinical Department for research, I really believe strongly in research.

At 51 years of age, I slipped on black ice on my driveway, breaking a leg in three places resulting in a full cast for five months. At 73, I had eye surgery for a detached retina resulting in no tennis, et cetera, for six months and severely limited activities. My current research program is administered very professionally and thoroughly by Carol Bolognese, to whom I am very grateful. Thank you.

DR. CARSON: Thank you.

Gladys Quinterro?

MS. QUINTERRO: Good afternoon. My name is Gladys Quinterro and I am a Hispanic American woman. I am single, retired, and live alone in Arlington, Virginia and I am a very active senior citizen. I volunteer most of my day for an Arlington senior center where I assist with activities including the

daily luncheons.

Everyday I see the effect of poor health and the consequences of becoming frail. People are afraid to come when it rains or they stop coming all together because they are afraid of falling and have fallen and have a fracture.

I also volunteer and participate in many cultural activities. I am very active. In general, I walk to the senior citizen center -- an hour and twenty minutes a day. I mostly use public transportation. I love to travel in the United States and abroad. Often, we might backpack.

In general, I am blessed with good health and I have a wonderful quality of life. Five years ago, I was told I have significant osteoporosis. I volunteered for research study in which I received a short every six months -- a shot every six months along with calcium and Vitamin D. I have a had quite a few falls, quite often, quite brutal, and have no broken bones. I went to classes to help me learn how to prevent falling. Also the medicine has helped me a great deal.

I am receiving most help -- all this medicine has protected me very well in my health. I am grateful for the five years I am able to do all activities and enjoy it.

In the program, I agreed to have a bone biopsy and hope that it will be shown that the medicine was safe and effective and for me and for anyone who will need to take it. Next week I will have another bone biopsy after five years of studies.

I thank you all on behalf of the women who have taken these injections to hopefully give women with osteoporosis an easy way to receive treatment and stay enjoying their quality of life. I have not received any financial support for these from anybody. I am a volunteer. I thank you.

DR. CARSON: Thank you.

Next is Laurel Glassman.

MS. GLASSMAN: Good afternoon. I am counsel to the law firm of White & Case, resident in the Washington, D.C. office. I have no affiliation or financial relationship to disclose. I am also a 60-year-old woman with osteoporosis. I was diagnosed

with osteopenia on my 50th birthday at menopause. This rapidly progressed to osteoporosis in two years.

Both of my grandmothers had osteoporosis. One died of the disease after breaking her hip. My mother died of breast cancer at 56, but by that age already was developing a dowager's hump. None of the medications I have taken for my osteoporosis over the past nine years appears to have worked for me and I am not a candidate for hormone replacement therapy.

These medications include Fosamax, Evista, Miacalcin, Actonel and Forteo. I was one of the 4 percent of patients on Forteo who did not show any increase in bone density after two years on the regimen. I'm currently still taking Actonel and Evista and watching my bone density continue to decline. For me and other people like me who have not had a positive response to currently available drugs for osteoporosis and over-the-counter Vitamin D, calcium plus weight bearing exercise, efforts to find and improve new drugs to effectively treat this disease are urgently needed.

I worry everyday about what osteoporosis

will mean for my long-term future and hope that the FDA will continue to approve medications such as denosumab, if proven to be safe and effective treatments for osteoporosis. Thank you.

DR. CARSON: Thank you.

The next presentation will be by Seth Ginsberg, president of the Global Healthy Living Foundation.

MR. GINSBERG: I have no disclosures to make today regarding my travel here. The Global Healthy Living Foundation and CreakyJoints does accept grants and donations from many pharmaceutical companies as well as government and private foundations.

Good afternoon. On behalf of the Global Healthy Living Foundation, a 501(c)(3) patient advocacy group, and specifically on behalf of CreakyJoints, the 32,000 member bone and joint disease community that is a part of a the Global Healthy Living Foundation, I'd like to thank the committee for allowing me to speak about osteoporosis, a globally recognized priority health issue with economic and quality of life costs equal to and sometimes greater

than many much better known diseases.

My name is Seth Ginsberg, a co-founder of CreakyJoints and the Global Healthy Living Foundation. I was diagnosed with spondyloarthropy at 13. By 15, I was a national spokesperson for the Arthritis Foundation. And at 18, when I went away to college, 200 miles from home, I quickly realized the need for a positive supporting community to share strength and experience with experts and other patients alike. CreakyJoints was the result of this need. Today, 10 years later, we have a vibrant community that participates in online as well as local community events held throughout the country.

It is in this outreach context that I am speaking here today, representing our members with bone loss whether it occurs from ablation therapy or post-menopausal osteoporosis. Our members are information seekers. They tend to have higher than normal compliance and seek individual initiatives in order to continually improve their quality of life.

Our members want to know what treatment options are available to them, how safe they are, how

much they cost, and how easy they are to take. We take their voices to the media, government, pharmaceutical companies, employers, third party payers, and the general public in an effort to educate, inform, and persuade these audiences to pay special attention to our community. This is why I am here today, to provide all the persuasion I can in support of denosumab and other new drugs that will expand the treatment options for doctors, patients, and caregivers to consider. Although I was not here earlier today, I am sure previous speakers have spoken much more authoratatively about the seriousness of this disease and the pressing need for pharmacological options, and in the case of ablation therapy, the first option.

The cost issue alone speaks to the critical need for a wide variety of treatment options. Early diagnosis and aggressive treatment are necessary in order to reduce the costs associated with fractures. These are unnecessary costs when treatments can improve bone mineral density.

Treatment can prevent fractures and the

economic cost and emotional trauma associated with osteoporosis. We've seen this firsthand. Ongoing education, a supportive environment, and individual initiatives, such as incorporating diet and exercise into a personal identity, are goals we try to reach at CreakyJoints.

We think government and industry can support us in this effort by continuing to monitor the effectiveness and safety of drugs our members rely on to extend studies post-introduction and to make the results of these studies public. Our members need this information and society is better off when data is continuously compiled and then made available.

In addition, because our members are above national compliance averages, we look closely at how they can maintain their health practice. We have found that a person must be logically and emotionally committed to managing disease, and they must believe their treatment protocols are right for them. Our members talk to us and it's our responsibility to bring their comments and stories to panels such as this one today.

But these are more than our members; these are our uncles and our aunts, our mothers and our fathers, our sisters, our boyfriends, our husbands and wives. So our responsibility today is large and it's up to me to convey their feelings in the three minutes I have remaining.

To quote one person, "all the women in my family have died from osteoporosis." A member from New Jersey told us yesterday on the phone, quote "I'm not yet post-menopausal, so I can't take any of these drugs, but I want the widest choice possible for when I can begin therapy." I quote, "I didn't know what osteoporosis was until I broke my hip 10 years ago." Said another member from Kansas City, Missouri, "I began to learn everything I could about options available and there weren't many. Today there are more. Tomorrow, I hope my daughter will have even better choices." Quote, "I work to supplement my Social Security and after my wrist fracture, I was unable to work as a cashier," says Ellen from Baltimore.

Ellen is 69 this year, and is back at work

but with limited range of motion in her wrists. She did not have a medical home at the time of her accident two years ago and was not on any bone strengthening medication. She is currently taking medication for her osteoporosis. Quote, "I wish I had paid attention to the medicine that was available, that could have helped prevent my broken wrist," she commented at an online patient event recently.

We know patients want choices and we know many patients are willing to do their homework so that they are well informed about their own osteoporosis. We also know that panels like this one are an important link between patients, physicians and medications. I hope I've been able to use my time efficiently today, and I hope I've represented our members throughout the United States by bringing their messages of a desire for new treatment options, a choice of how and when they take their drugs and how hard they are willing to work to make sure they stay informed, stay healthy, and stay active.

Thank you again, Madam Chairman, for the opportunity and for allowing the Global Healthy Living

Foundation and CreakyJoints to speak today. I look forward to working with you all in the future. Thank you.

DR. CARSON: Thank you.

Is Ellen Summers (ph) here?

Okay. Our last presentation, then, will be by Cynthia Pearson, Executive Director of National Women's Health.

MS. PEARSON: National Women's Health Network, thank you. I didn't receive any support for my travel here today. I'm local, and the organization I represent, National Women's Health Network, is a women's health consumer organization that's supported by contributions from thousands of individuals across the country and some foundation grants.

By choice, we don't accept any financial support from the medical industry. And I'm here to urge caution, which is very different from everything else you heard during the open public part of this meeting today. Everyone else has spoken either about the need for more awareness, the need for more treatment options, the need for more information. And

I think the fact that my urging caution seems contradictory to those other comments, is a reflection on the history of what's happened with osteoporosis in the United States over the last 25 years.

In my remarks, I'm going to concentrate -- you have to answer questions about two very different populations -- about post-menopausal women and about cancer patients. I'm going to concentrate my remarks on post-menopausal women as fits our role as the Women's Health Network. If any committee member wants to ask me at the end of my remarks, I can say something brief about our reaction about cancer patients.

But to my point about what has been the history of the awareness of and the ability to adequately respond to women's needs for good treatment and support around osteoporosis. Well, I would say 25 years ago, and probably many of the researchers who are here would vehemently agree, that at that time in the 1970s and the early 1980s, there was far too little awareness; that a combination of, I'll call it sexism and ageism, left many older women in painful

situations with vertebral crush fractures that were just thought to be -- they were told was part of old age, or with a hip fracture that hadn't been perceived as a risk in advance and wasn't prevented.

Thanks to many of the researchers who've been so active over a long time and caring clinicians and some voices from the women's health community, that's changed and we now have a time when there is more attention, more research, more diagnostic tools and more treatment alternatives, and that's a good thing.

I also want to acknowledge this sponsor's role as a new player in the world of osteoporosis treatment research, and in the very good job they did in including women of color, which is a step forward. Many previous trials haven't been as good on that. And by making a very special effort to get a high percent of women, 70 years and older, into their fracture trial to test their drug in the population for whom it could have potentially the most benefit.

But in addition to this good progress we've made at recognizing that osteoporosis is an important

public health concern for many older women, in our opinion, there has been over diagnosis, over treatment and unnecessary harm. So just two ways I want to illustrate that.

One is that the current FDA guidelines, as we all heard this morning, for testing a drug for use by healthy women to reduce their risk of fracture in the future, means that the guidelines only require evidence that the effectiveness of the drug is seen on x-ray; that a woman can come into this study with no symptoms, she can leave the study with no symptoms, and the FDA can find enough evidence of benefit to say that it works by their guidelines.

Current screening guidelines, which might be the entry for a woman into that study or after approval into the group for whom the drug could be prescribed as a preventive strategy-- current screening guidelines that are evidence-based are actually calling for screening for women starting at age 65. Those are from the U.S. Preventive Health Service Task Force.

Unfortunately, what we saw even here in this

room with our own public health agency, the FDA, is that there is a much too common impression created by very effective marketing campaigns that screening should start at age 50. So I went into those two things in some detail to just provide you the context that we see, that many women are getting screened who don't need it and that the FDA, who has to find some sort of guidelines for what studies they require, has guidelines that are so expansive that the question that was asked and not really answered this morning about how many women are needed to treat, the answer is pretty large.

With those rules for testing and the common misperception that screening should start at age 50, the number of women who need to be treated to get an effect and to see a benefit, to prevent one fracture that might -- even one fracture at all, but one fracture that might actually cause problems is pretty high. So if that number needed to treat is pretty high, then the safety questions become very important.

I'm seeing my sum up light, so I'll just sum up. As I heard this morning, listening to all the

presentations and as I read yesterday when I downloaded all the data that was online, we see an evidence of increased recurrence of breast cancer in cancer patients, increased occurrence of new cancers, including ovarian and cervical in post-menopausal women, increase of serious infections some of which required hospitalization. And both of these things, cancer and infection, are biologically plausible, as we heard -- as a cause and effect as we heard earlier this morning. And then there's the possibility of bone problems in the future.

So to really sum up, the FDA is going to ask you advisors at the end of the day to answer the questions that are attached to the agenda. And the questions go to, is there a reasonable expectation of benefit that outweighs the harm? And I would say looking at it from this perspective --

DR. CARSON: Thank you very much.

Thank you all for taking the time to prepare your comments, submit them, and of course, travel to present to us today. I'm always humbled by those who are willing to share the intimate details of their own

personal medical history for the benefit of everybody.

The open public hearing portion of this meeting has now concluded and we will no longer take comments from the audience. The committee will now turn its attention to address the task at hand, which is the careful consideration of the data before the committee as well as the public comments.

So let's go back to the question and answer session. I know we have a few left in the queue from before lunch.

Dr. Gut?

DR. GUT: Thank you very much, Dr. Carson. The sponsor conducted a really impressive development program with more than 30 clinical studies and more than 10,000 patients looking at efficacy and safety, but also pharmacokinetic and pharmacodynamics of denosumab. I'm interested in the safety profile in comparison in your two head-to-head Phase 3 trials with alendronate. So if you can please comment on the various events rates in those trials.

DR. EISENBERG: I'm sorry. I didn't quite hear the question. I apologize.

DR. GUT: Safety profile comparison in your two Phase 3 head-to-head trials with alendronate.

DR. EISENBERG: The alendronate comparison studies and the safety profile.

I think Dr. San Martin would be most appropriate to answer that since he conducted those studies.

DR. SAN MARTIN: As you said, we did two different comparison studies of denosumab versus alendronate. One was in the novel patients, 1,100 patients were randomized to either receive denosumab or alendronate and followed for one year.

The other study was in patient previously treated with alendronate for about three years and then they switched to either continuing alendronate or received denosumab. Both studies were double-blind and there was no difference in any adverse event or serious adverse event that can be discriminated between alendronate and denosumab.

The primary endpoint was changed in bone mineral density of the hip and secondary endpoints of the spine, and in both endpoints, in both study there

was a significant improvement in bone mineral density that favored denosumab versus alendronate. In terms of safety, there was no difference in any AE or serious adverse event that were remarkable.

DR. GUT: Thank you very much.

DR. CARSON: Mr. Goozner?

MR. GOOZNER: Thank you. This gets to the summary of serious adverse events. At several points in the company's presentation, you said that they were roughly equal, and you gave some numbers. But I had some questions when I was reading the materials before today's meeting about Table 18 that was on Page 83 of the submission, where there were a number of serious adverse events that were listed there that included like femur fracture and femoral neck fracture.

I was just curious. Why are those added in under serious adverse events? Aren't those events related to treatment itself? In other words, the reduction in those events that we saw with denosumab, isn't that a result of treatment?

And so if we add those into the -- my question becomes, if we add those into the serious

adverse events, doesn't that sort of inflate the number that's on the -- or deflate the number that's on the denosumab side?

DR. EISENBERG: So let me see.

Do we have the table from the briefing book? We can bring that up.

But in terms of fracture endpoints, all fracture endpoints are captured in this study, so we don't discount any fracture endpoints whether they're reported as a serious adverse event from the fracture endpoint. So it wouldn't impact that. If we can bring the table up so I'm certain to answer your questions properly. Thank you.

So with respect to the question you've have raised, there were events that do get reported as serious adverse events, and that's based on the investigator reporting. So the process there is if the investigator reports this event as a serious adverse event for the reasons FDA highlighted, the patient would have been hospitalized obviously, we would capture that. But all fractures are captured in the endpoint, so you're just looking at two different

perspectives on this.

MR. GOOZNER: So what I want to do is I want to understand what is the difference in serious adverse events between placebo and drug. And so doesn't it make sense in creating that chart to back out the numbers that are drug related to the primary and secondary endpoints in the trial, so that I get a fair picture of other than drug related events.

DR. EISENBERG: I'm not sure I entirely understand the question.

MR. GOOZNER: In all honesty, I think the FDA did the same thing in their presentation, and I was very confused about this when I was reading it prior to the meeting, so I'm trying to get clarification now.

DR. CARSON: The standard way in which we -- the FDA and all other pharmaceutical companies and academic institutions that capture adverse events is to display every adverse event and serious adverse event, regardless of whether they're at the endpoint of the study. Then when one analyzes not just the aggregate adverse events and serious adverse events,

one digs down into the variety of different terms in order to get an understanding of a variety of different adverse events that have been captured in the study, and that's what's been done here.

In fact, if we didn't actually capture those adverse events and serious adverse events of fracture, then we wouldn't be necessarily fully representing the safety profile. For example, if there was a therapeutic that actually increased your risk of fracture, then you would want to be able to capture in your adverse event database.

MR. EISEMBERG: In thinking about your question, I understand your confusion. So I think I understand it and it's actually a standard way in which we approach assessing for an adverse drug reaction, is what I think you're thinking about. And that assessment is to look at adverse events that occur in placebo versus your treatment, and then to say if it -- and the standard way of approaching is to say if it occurs in 1 percent more of your treated patients than your non-treated patients, that might be a real adverse event, or if there is a medical reason

based on causality or an unusual number of events to pay attention to it, then you assume that that's a drug related event. And we do those analyses of adverse drug reactions. And I don't know if we have -- we didn't present that in that way today. You saw all the data for both arms.

I can tell you the adverse drug reactions that I highlighted as those observed; so eczema, cataracts, and several infections of adverse events. infectious terms, the bacterial infections, UTI, the diverticulitis we commented on -- those events were of greater frequency in the denosumab treated patients than the placebo patients.

So we would consider those, as we've highlighted -- if we bring the slide up, 87, and I've highlighted those, the skin infection, latent hospitalization, hypocalcemia. Clearly, each one of these events we would consider from a pharmacovigilance safety perspective to be an adverse drug reaction, which I think is what you're asking. I'm not sure if I've gotten your question answered yet, but I think that is what you're asking.

MR. GOOZNER: I think that gets to it. I'm trying to in my own mind create what serious adverse events are drug related and what are specific, as opposed to a global score that sort of balances the two and says that they're about equal, placebo versus drug, when in fact, a lot of the adverse events were actually caused by the drug being effective.

DR. EISENBERG: Again, causality, just to be clear, we take a -- since we never really know causality unless there's a very clear understanding of mechanism, we actually don't bias our assessment by making a decision as to whether an adverse drug reaction is causal or not.

So for example, with cataracts, we consider that an adverse drug reaction because the numbers are different.

Do we have an explanation? No. Could it be due to chance? Yes. But we still would list that. We still believe that would be an adverse drug reaction. So causality is not an underpinning of making that determination. We simply objectively look at the differences. And what I highlighted for you in

the slide are those events that are objectively different between the two groups.

DR. CARSON: Thank you.

Dr. Collins?

DR. COLLINS: I just wanted to reiterate, I think that this degree of suppression that we see both in terms of bone markers and on histomorphometry, I remain pretty concerned that this is really a signal of long-term problems, as you do. And it's reassuring to know that you have studies in place that will pick up on this. And we did hear though that already in other studies with this drug, in cancer patients, that some cases of osteonecrosis of the jaw have begun to appear.

Any subtrochanteric fractures either in this study or the cancer studies?

DR. EISENBERG: There were three in the placebo group. That's the only cases that we have.

DR. COLLINS: So then in terms of the long-term follow-up studies, that if these do begin to appear, and I don't know if this is a question for you or for the FDA, what are the sort of criteria for a

sort of exit strategy of what will signal a real concern about this, and what actions will be taken in regard to this?

DR. EISENBERG: Well I can comment briefly as to how we've thought about the long-term safety assessment. We will be acquiring data in a broad number of studies as well as the other pharmacovigilance studies. We communicate this information on a regular basis. So safety updates, for example, that are comprehensive are provided to regulators more frequently when a drug is first approved and at least annually thereafter.

Any of the studies that we commit to that have endpoints get recorded as soon as those data are available, and we make those data available immediately. I think one of the aspects that's unique to denosumab is should we see a signal or should there even be a concern in an individual patient to the signal, it is reversible.

DR. COLLINS: Right. And that's very comforting, which isn't the case with the biphosphonates. But one of the things I wonder too --

I mean, is really this degree of suppression really necessary to get the effect that you want? Could less frequent dosing or a lower dose achieve the same protection with a lower risk of some of these things we're talking about, ONJ, et cetera?

DR. EISENBERG: If you'd like, we could walk through the data in detail. I can tell at a high level that in most of what you see in terms of the pharmacodynamic profile of denosumab is that all of the doses that we looked at in our Phase 2 studies suppressed the markers immediately. Much of the difference really relates to how long a period you want to have between the doses. So the six-month dosing interval was selected based on a dosing interval that was felt to be both convenient. And, also, at the end of the interval we actually saw some slight increase in the CTX marker, suggesting it wasn't an over suppression effect.

So six months was selected that way. We're happy to walk through, if you'd like to look at the data at shorter dosing intervals, but that's the basic rationale.

DR. ROSEN: Could you walk through the Phase 2 on that point for us, because I'm a little confused about why you selected 60 milligrams every six months versus the 14 milligrams that gave the increase in spine bone density in the Phase 2 dose ranging study.

DR. EISENBERG: Let me have Dr. Stehman-Breen comment on that.

DR. STEHMAN-BREEN: So the goal in identifying the dose was to be able to provide the lowest dose with the maximal increase in bone mineral density that could be given at the least frequent dosing interval. And as you've probably noticed from your briefing document, we assess a large number of different doses and two different dosing frequencies.

It was, as you can imagine, a very significant decision in terms of choosing the dose. And so let me walk you through a little bit of data to help you understand a little bit better what our rationale was.

So these are some data from the Phase 2 study. And on the left side of the figure, you can

see the mean CTX values, which are on the percent change from baseline, is on the vertical axis with time on the horizontal axis.

What you can see is that the 30 every three months, the 60 every six months, and the hundred-and-two-ten every six months had generally the same levels of suppression of CTX with a little bit of attenuation at the dosing interval with 60 milligrams every six months. The 14 milligrams every six month dose didn't appear to have adequate suppression of CTX.

DR. EMERSON: This graph doesn't include the 14 milligrams every three months.

DR. STEHMAN-BREEN: I promise I'll get there in a minute, Dr. Emerson.

DR. EMERSON: Okay.

DR. STEHMAN-BREEN: So if you look at the right side of the figure, you can see bone mineral densities, and these were --

DR. EMERSON: Can I just interrupt for a second --

DR. STEHMAN-BREEN: Sure.

DR. EMERSON: -- and ask you, when you say

not adequate suppression, what are you referring to? Because it states 14 every six months, it goes down to 80 percent and then comes up 40 percent suppression. So what's your definition of adequate suppression?

DR. STEHMAN-BREEN: So that's a great observation. As Dr. Eisenberg pointed out, all of the doses result in the same maximal level of suppression and the difference is really the duration of that suppression.

Now if you look on the right side of the figure, you can see the percent change in baseline and bone mineral density and you can see that that 14 milligrams every six month dose did not provide significant increases in bone mineral density, as highlighted by the white dot, as the other doses did.

DR. EMERSON: But that's hip. That's not spine, that's hip, right?

DR. STEHMAN-BREEN: That's hip.

DR. EMERSON: But spine was four-and-a-half.

DR. STEHMAN-BREEN: Yeah. So I'm going to show you some more data in just a minute. And again, as you can imagine, there was a tremendous amount of

information that needed to be digested in making this decision.

These are the bone mineral density changes at 24 months for all of the doses that we assessed. And I know it's a bit of a complex figure, but if you focus on the 14 milligrams every three month dose, which is in grey, and the 60 milligram every six month dose that's in yellow, you can see that there are some differences depending on where you measure, the lumbar spine, the total hip, or the trochanter. And when we assess the totality of the data, the 60 milligrams every six month dose appeared to have greater increases in bone mineral density and we could use it at a less frequent dose interval.

And importantly, it had that slight attenuation at the end of the dosing interval, which was felt to be a desirable effect with a little bit of a release or return of osteoclast function at the end of the dosing interval.

So we were balancing two things here. We were balancing not having over suppression without having too much release of osteoclast function, which

one might be concerned that there would be over activity of the osteoclasts with potential adverse events related to that.

So this dose provided the greatest balance of increases in bone mineral density, but again allowing a little bit of release at the end of the dosing interval and allowing that six month dosing interval, which was felt to potentially help with adherence of the drug, which as you heard from Dr. Siris, is an important problem in osteoporosis.

Did that answer the question?

DR. CARSON: Dr. Emerson, are you happy with the answer?

DR. EMERSON: Well, if you look at that last graph and you look at the six milligrams every three months, that's also looking fairly good. And so I think the statements that it's clear that this is the lowest dose is not there. Although I do wonder at the sort of vacation idea, that by having the high dose, whether you're effectively giving the patients a vacation from the drug for a little while and still getting the bone mineral density, but I can imagine

that would be beneficial.

DR. CARSON: Dr. Rosen?

DR. ROSEN: I think it's very hard, retrospectively, to go back and say you picked the right dose, so therefore you picked the right dose. And it's very hard for us to second-guess that. I mean, obviously, there were a number of things that went into that sort of decision-making. But I am surprised a bit that the lowest optimal dose actually is significantly lower.

DR. CARSON: Dr. Nelson?

DR. NELSON: Yeah, I had questions about the over suppression also.

What's the longest you've had any patients on this?

DR. STEHMAN-BREEN: We have subjects that have been on denosumab for more than six years, that were part of our Phase 2 study.

DR. NELSON: And is there a plateau in the bone density accrual or is it just keeps going up?

DR. STEHMAN-BREEN: No, there isn't, and if we can bring up that slide, you'll see that there are

continued increases in bone mineral densities out to 72 months. And that's illustrated by the yellow dotted line here.

DR. NELSON: And I also had a question about the holiday period. It seems to me like it would be quite beneficial because you have a perfect setup here where you have a recovery over a short time frame. So have you looked specifically at what are the effects of holidays in terms of accruing bone density? And is there maybe a better paradigm here for taking advantage of both sides of this equation?

DR. STEHMAN-BREEN: Well, we feel that what we tested is the data that I've shown; what we've assessed in clinical trials. And we haven't assessed, for example, longer dosing intervals. But again, this is a balance between the right level of suppression without what there has been identified as an area of observation or an area of concern, which is too much release at the end of the dosing interval, where you'd have suppression of bone turnover followed by a robust increase in osteoclast function.

So in balancing that, we've ultimately ended

up with a dose that provides significant reductions in bone turnover at the beginning of the dosing interval and then, again, some release at the end of the dosing interval. And with our three years of fracture data, in addition to the prostate cancer study with hormone ablation therapy, has demonstrated very robust reductions in fracture risk.

Now as was pointed out, we've very committed to continuing to understand our long-term safety profile and we feel that we can effectively do that with our large extension study in addition to the variety of other studies that Dr. Eisenberg outlined and our large set of observational studies.

DR. CARSON: Okay.

Dr. Gulley?

DR. GULLEY: Yes, thank you. So my question was regarding the 138 Study, the prostate cancer. So realizing that this is a heterogeneous patient population with biochemical failure on hormonal therapy, the one slide that was looking at the assessment of PSA antigen -- I believe slide 60 -- that slide seemed to show no difference between the

two groups. But was there any another look at PSAs in terms of either PSA velocity, PSA doubling time, time to castration resistance that was looked at in this study to help us understand perhaps differences in progression?

DR. EISENBERG: Well let me ask Dr. Matthew Smith, who was the principal investigator of that study, to comment and maybe we could bring up slide 60 so that that's available for comment.

DR. SMITH: So I'm Matthew Smith, a prostate medical oncologist from Massachusetts General Hospital and the P.I. for the prostate HALT study. So I think what you're raising is the issue of sort of potential concern about that this therapy would impact underlying cancer control. The study had pre-specified ways to look at this. There are three ways. One is PSA progression, one is bone scan progression, and the other is overall survival. And really, by all of those metrics, there is no signal to suggest greater cancer progression.

So you see that one way here, which is looking at really -- this effectively is showing in

the slide there, the time to progression to castration resistance. Because what we're looking at here in the bar graphs is the proportion of patients who meet those PSA metrics despite a castrate level of testosterone.

So I think what you can appreciate there is there's really no suggestion using early sensitive PSA criteria of greater cancer progression. So we find that quite comforting.

Dr. Kehoe nicely pointed out -- though that as you'd expect in a population of hormone sensitive patients, there were very few deaths, as you again would expect in this favorable population. We actually believe that the drug may in fact, delay or prevent of the development of metastatic disease to bone. And we're testing that hypothesis in a population of high risk patients with castration resistent disease.

DR. GULLEY: And just as a follow up, there was very few number of patients that had actual metastatic disease to bone.

Is that correct?

DR. SMITH: Right. So again, three ways we looked. The PSA, which would be -- and as most of the audience would know, PSA while it has its controversies in screening, is a very reliable marker of cancer progression. So uniformly, patients would progress by PSA before developing radiographic or clinical progression. So in this study, in a pre-specified manner, we also looked at bone scan progression and there are no discernible differences. Although again, the rates of significant bone scan abnormalities was only about 5 percent at three years on both groups.

DR. CARSON: You may as well just stay up there because I also had -- are you sure that the PSA is as predictive of the spread of disease in a population treated with monoclonal antibodies, as it is in one who's not treated with biological products?

DR. SMITH: Well the specificity of the antibody would -- if your question would be the concern that it would interfere with PSA measurement, I believe there's absolutely no concern about that. Perhaps someone else could address that.

DR. CARSON: Not measurement, but rather release or change in the biologic -- I mean is it as predictive in that?

DR. SMITH: Well, again, we're not relying solely on PSA here. So to answer your question, I don't know how you would know except by doing the clinical trial. So I think there's supportive data, not just PSA, although again, that would be earliest and most sensitive indication of disease progression. There's absolutely no detrimental effect on bone scan progression at three years. And as you saw in slide 61, overall survival was -- there's absolute similarity of overall survival.

DR. CARSON: The second question that I had was, were those patients who developed cataracts treated differently for their prostate cancer than those patients who did not develop cataracts?

DR. EISENBERG: We looked at the cataract factors, patient related factors. We honestly can't find anything that gives us any comfort that we understand the signal.

DR. CARSON: Dr. Uzel?

DR. UZEL: Hi. My question is regarding the infections that led to SAEs.

Did any of those patients who had life-threatening infections or serious infections were also on disease modifying agents or other immunomodulatory drugs given this patient population, or were they neutropenic? Are there any other co-morbidities or other factors that may have led to these infections?

DR. EISENBERG: I don't think if we look across the serious infections, maybe Dr. Stehman-Breen will comment, that in the totality of all infections, that we saw any factors that we would consider confounding in terms of other treatments. And as we noted, certainly the opportunistic infections, viral infections that typically would be associated with those kind of immune modifying drugs were actually more frequent, was no difference between the two groups I guess is the fairest way to state it.

DR. UZEL: My second question is I understand the data about the immunogenicity of this drug and it's predicted to be very little in the future, but if patients or the physicians report to

you a significant concern about immunogenicity, will you be able to provide assay or help these physicians, patients to detect if there's any other antibody formation?

DR. EISENBERG: Oh, absolutely. Amgen has actually a very significant effort to ensure that if antibodies develop, we can provide assays and determine whether they're neutralizing and provide additional information?

DR. UZEL: Thanks.

DR. CARSON: Dr. Buzdar?

DR. BUZDAR: Yeah, the question which I have is that here the indication, which is being sought, is for treatment of osteoporosis, prevention of osteoporosis and patients who are cancer therapy getting therapies which are affecting the bone turnover, slowing that down. And on the downside when we look at it, that it does increase the risk of developing some cancers, at least there is some hint of it, some hint of causing increased infection, some hint of causing the other serious side effects.

Question is, have you looked at it or

developed some kind of a model in which you can predict that in the overall therapy, the ratio will be favorable? That i.e., preventing a major life changing event like a fracture of the hip versus developing a lung cancer or a breast cancer or an ovarian cancer, which is also a major life changing event and far more lethal than a hip fracture.

DR. EISENBERG: Well certainly -- I mean, part of this is what the level of incidence is. So I think, first, if you start to look at how you weigh small differences that don't reach statistical significance, I'd remind you to start that the overall benefit in terms of survival actually favors denosumab. If we then ask the question of the number of fractures, absolute number of fractures that occurred, that signal is quite strong.

Now can I tell you from the percentage of patients who have a hip fracture, how many lives we would save; no, I think that would be presumptuous, though the number of fractures that are prevented and the number needed to treat to prevent those fractures is actually quite low, and my recollection is

somewhere around one in 30 would be patients treatable -- will be prevented from having a fracture.

Now if you then ask the question -- again, keeping in mind that if you look overall when we do these number needed to treat, number needed to harm, we usually don't look at statistically insignificant differences on the harm side. We look at data that are confirmed.

So I think your point is fair that there are potentially risks that we have to monitor long-term, but none of those have been confirmed. Some cancers were actually less with denosumab treatment. And so I think it's a little difficult for me to answer that question with respect to an absolute risk, since one has not been demonstrated in that regard. I think in terms of the skin infection risk, we have a little more concern. But most of the other risks don't reach -- none of them reach statistical significance. None of them are more than small differences.

DR. BUZDAR: Yeah, but I'm not concerned about skin infection, which is easily treatable. I am more concerned about ovarian cancer, which is almost

numerically is doubled.

DR. EISENBERG: That's a fair point and --

DR. BUZDAR: Because the thing is, that is life threatening, potentially lethal disease, almost in majority of patients. So the thing is we can't say that, oh, we will see how the data evolves in the data there too. I think this data, if somebody wants to sit and think about it, should be able to calculate what is the net benefit taking into account.

Because the thing is, if you're trying to expose a huge number of patient population to a therapy which is increasing, even a small but subtle increase in potentially life changing events, you have to calculate what is the therapeutic index of the therapy in the long run?

DR. EISENBERG: Did you want to say something to that?

The only comment I'd make is, one, that it is has to be confirmed. So ovarian cancer actually was one that since we were quite interested in reviewing the safety, I reviewed and compared to other trials, a comparable trial. Just to give you a

perspective on this, our estimates and malignancy rates in trials are rarely very exact.

So for example, the RUTH trial with raloxifene, which is very large, similar patient population, 10,000 patients, 10,000 women treated with raloxifene or placebo, so placebo controlled. Not a fracture trial. There were excesses both in endometrial and ovarian cancers in small numbers. I highlight that only because the integrated safety databases for raloxifene are very clear. There is no risk.

So when we're looking at small numbers, to count nine versus five in an isolated sample set really doesn't provide an absolute estimate of risk. I think we should restrict our estimates of risk to what's statistically significant and demonstrated in the data we're showing you.

DR. CARSON: Dr. Margolis?

DR. MARGOLIS: Thank you. I just have a quick clarification of a slide that Dr. Eisenberg showed near the end. You were talking about a safety study of 380,000 individuals and then showed a slide

looking at two databases, one of which is a medical records database of 120,000 and 160,000 individuals.

Did you mean that you're going to do a study yourself, de novo, or are you going to have a prospective cohort study of 380,000 individuals that you're enrolling, or are you going to do a bunch of database studies that in total have observations on as many as 380,000 individuals?

DR. EISENBERG: No. Our intent obviously since we have the advantage that when denosumab -- assuming denosumab's approved and enters into the market, we can get a de novo cohort, is to accrue a de novo cohort. And we base those numbers on the number of women in those databases who have post-menopausal osteoporosis are treated with other therapies.

Then a very conservative assumption, that somewhere in the order of 5 percent -- or 10 percent of patients who are currently treated might be treated with denosumab, and then an accrual time of five or six years.

But the number is based on a prospectively

defined cohort to allow an assessment of risk as low as one in 100,000.

DR. MARGOLIS: I'm still confused. So it's 380,000 people that will be in a cohort that's represented within those data sets; not a cohort where you're deciding what data you're collecting. You're deciding what other tests you're doing. It's a prospective --

DR. EISENBERG: It's within the -- yes, absolutely. We would look to --

DR. MARGOLIS: It's within those other studies. Other people would be determining reason to treat.

DR. EISENBERG: Right.

DR. MARGOLIS: What follow ups they're going to do.

DR. EISENBERG: Exactly. It's the standard approach, yes.

DR. MARGOLIS: Okay.

DR. CARSON: Thank you.

Let me also remind the panel that we will have time to discuss, so let's just try to get the

information that you feel is missing from the sponsor.

Dr. Johnson?

DR. JOHNSON: Thank you. Because we're being asked to look at specific indications and being asked questions in regards to them, looking at your HALT study in women with breast cancer, can you give me some information on the sample number that was chosen? Because it's significantly less than we see certainly in the prostate study, and certainly many less than in the PMO study.

Also, the length of time for that study, I think it was limited initially to two years and that's all the data that we have. I know you're extending it out, but it seems like this is somewhat smaller and shorter than your previous studies.

Can you explain this?

DR. EISENBERG: Certainly. The design of that study, as I highlighted actually in my opening comments, was specifically powered to look at bone mineral density. Since, as FDA highlighted, once a novel agent that improves bone mineral density and bone strength has been demonstrated to reduce

fractures, then it's considered confirmatory to look at bone mineral density in subsequent studies. So both the prevention breast cancer study and the prevention HALT study actually are similarly sized.

Now we did have a different approach in the study in men, and the reason for that is simple. There are no large-scale studies of osteoporosis treatment or bone loss treatment in men. So the rationale there, really in collaboration with Dr. Smith and others was, let's do a study in that population which really has never been studied to the extent that women with post-menopausal osteoporosis and bone loss have been studied, that's sufficiently large to allow a secondary endpoint of fracture prevention. That's the rationale.

DR. CARSON: Dr. Richardson?

DR. RICHARDSON: The preamble to the applicant's information talked about some of the other factors that are important in bone health, including some of the lifestyle influences, smoking, diet, exercise, alcohol intake. And it would be great someday to see just what those have as an impact on

bone mineral density.

I understand the numbers are not thought to be particularly reliable in the studies that have been done, but these things obviously vary a great deal around the globe also. And I'm curious whether you stratified for any of these factors in your studies?

DR. EISENBERG: We didn't stratify.

I don't know, Dr. San Martin, if you have any comment.

Just sort of background demographics, I think we're very balanced with respect to all those factors, I don't know -- the smoking and other things that we would have highlighted.

DR. RICHARDSON: You mean you collected the information?

DR. EISENBERG: Yes, we collect that information, much of it.

DR. SAN MARTIN: We did collect all the information that is used to score the patients using the FRAX tool, and we stratify by age, which is a more important risk factor for fracture. And the bone mineral density increase is very similar across all

the baseline categories you mentioned.

DR. RICHARDSON: Well then maybe you could tell me how the randomization was carried out. Was this done in a central office where as these patients were entered, they were randomized at that time, or were they randomized within countries?

I mean they're -- for example, the smoking rates vary a great deal from country to country. Eastern Europe has very high smoking rates these days.

How was that randomization done?

DR. EISENBERG: Let me ask the principal investigator of the study. Dr. Cummings can perhaps comment if he's -- or actually Steve Snappin, the statistician, can comment on randomization.

DR. RICHARDSON: My point with this is, is there a reason that the placebo arm had more lung cancers and more fractures? I mean did you have more smokers randomized to the placebo arm, for example?

DR. EISENBERG: I'll ask Dr. Snappin to comment. He's the statistician who's been involved in analysis.

DR. SNAPPIN: Steve Snappin from

Biostatistics. I can just comment on how the randomization was done. It was a central randomization system using and IVRS, or interactive voice response system, stratified only by age category. So four age categories, and the women were randomly assigned treatment groups within each of the four age categories.

DR. RICHARDSON: So the answer is, no, you don't know.

DR. EISENBERG: All the factors appear completely balanced between the two groups as far as we can tell.

DR. RICHARDSON: No, you don't know, it sounds like.

DR. EISENBERG: No, we do know.

DR. CARSON: Did you look at the various factors, lifestyle factors, mentioned between those two groups after stratification or after randomization?

DR. STEHMAN-BREEN: So randomization was quite effective and all of the factors you outlined were balanced across groups. The lower incidence of

lung cancer that was observed in the denosumab group, we have attributed it to chance. And again, it's not unexpected that in a randomized trial, you would have small numerical imbalances in certain types of cancers.

In this study we had numerical imbalances that favor denosumab in lung cancer; malignant melanoma, that were as large as the imbalances that we saw for example with ovarian cancer. This is very typical of a randomized trial, even of this size.

DR. SAN MARTIN: I guess the other piece of information that may help is that the randomization blocks were four, so that takes care of any type of imbalance by region. So it's unlikely to see any imbalance.

DR. CARSON: Dr. Richardson, any other questions?

DR. RICHARDSON: No, thanks.

DR. CARSON: Dr. Emerson?

DR. EMERSON: Just to follow up a little bit on maybe what can seem like our preoccupation with these risks that, as you say, are not statistically

significant. But statistics means never to have you're certain and it's what we're scared off. But you made reference to a number needed to treat.

Can you elaborate upon that?

DR. EISENBERG: Sure.

DR. EMERSON: Both in terms of the treatment of osteoporosis and the prevention.

DR. EISENBERG: Yes, we can. I have a slide in terms of number needed to treat.

This is for the treatment indication. This simply shows you the difference, as you'd expect, based on the absolute rates, so for each of the fractures, the pre-specified and other fractures.

Also, we identified the higher risk patients, older patients, and clearly since they're at higher risk of hip fracture, that tends to be over weighted in terms of bringing you down to a smaller number. I believe actually in response to your --

DR. EMERSON: And this is osteoporosis?

DR. EISENBERG: This is osteoporosis.

DR. EMERSON: And this is treatment --

DR. EISENBERG: Treatment. And then in

response to your question before the break, Dr. Snappin, I think you went and calculated the data for prevention, right?

DR. SNAPPIN: Yeah. So just to clarify on the numbers that were just on the screen, that refers to the numbers of women treated for three years, the duration of the trial. And just to give a rough sense, you asked a question earlier in the morning about cohort of women at somewhat lower risk, let's say. And I think the example was at a risk of 15 per 1,000 per year. And what would be the number needed to treat in that case.

Obviously, we can't answer directly because we haven't done the study, but you can get I think a sense of what the numbers needed to treat would be. If you imagine that if the rate is 15 per thousand, the drug effect is something like a prevention of two thirds of the events, meaning 10 per 1,000 would be prevented in on year. Over three years to correspond to the duration of the trials that we did, that would be 30 per 1,000, resulting in and NNT of about 33, just as a rough guess.

DR. EMERSON: For any fracture, a 33? Just because this is going to figure in, just to make certain it agrees, I also find for prostate cancer, I agree with your numbers that you just put up there and I come up with about 50 needed to treat for the prostate cancer. Would that be --

DR. SNAPPIN: Correct. We calculated something in the forties, correct?

DR. EISENBERG: And I think it's important because when I calculated that number, I also looked at the population, and it is a low risk in mixed population. And Dr. Smith can certainly comment. So it wasn't a population necessarily picked for a high risk of fracture for prostate.

DR. EMERSON: And another real quick question is, that's any fracture. And so we've got a whole lot of fractures, and you're picking out -- some of the definition of your fractures are quite subclinical. So in terms of your vertebral fractures of looking for an increase in the amount of existing fracture, you call it a new fracture.

Do we have a feel for -- the hip fracture is

clearly significant, clinically, but --.

DR. EISENBERG: I mean the pre-specified endpoint is the most robust obviously because of ascertainment and predefined criteria.

But Dr. Stehman-Breen, you may want to comment in terms of other fractures. Many are symptomatic in terms of vertebral fractures.

DR. STEHMAN-BREEN: Yes. Vertebral fractures are often asymptomatic in that women don't realize they've had those fractures. But over time, they really do contribute -- as we've heard from one of public speakers and others, they contribute to a significant amount of morbidity in women as they get older.

DR. CARSON: Mr. Goozner?

MR. GOOZNER: I was actually going to ask about the number needed to treat, and they've answered the question. I would only just add that, that slide that you just threw up there should have been in the original briefing materials, in my humble opinion.

DR. CARSON: Dr. Rosen?

DR. ROSEN: Yeah, I'd like to revisit NNT

for the prevention arm.

So you're telling me that you can't really -- the number of fractures in the prevention arm was relatively low. I think there were six in one arm and -- so you're telling me that the NNT for these low risk individuals was 33 for the denosumab treated individuals?

DR. SNAPPIN: No, this --

DR. ROSEN: Yeah, you can't say that, right?

DR. SNAPPIN: Cannot say that.

DR. ROSEN: You cannot say that. We need to clarify that.

DR. SNAPPIN: Correct. We were talking hypothetically about a population with a risk of 15 per 1,000.

DR. ROSEN: Right. But that may clearly not be the case, since the T-score is minus 1.5 and these individuals were not high risk individuals. I wanted to ask the group -- incidentally, I thought the presentation was excellent. And I'm not trying to be critical, but I'm trying to explore things that are important for this committee.

I wanted to ask the group -- and maybe Dr. Cummings can comment on this.

The fracture risk reduction in the non-vertebral fractures was 20 percent with denosumab, and that's with a hip bone density that's much higher than what you see with other treatments, and clearly spine bone density much higher. And that's about where the newer data look like in terms of meta-analysis.

So if a lot of what you're basing your studies on are change in BMD, why are you only getting about the same risk reduction as you would with every other treatment that we have available?

DR. EISENBERG: Yeah, I think Dr. Cummings would like to respond --

DR. CUMMINGS: Dr. Steve Cummings. I was principal investigator and leader of the Steering Committee for the Freedom trial, and Professor of Medicine, Epidemiology and Biostatistics Emeritus at the University of California, San Francisco.

As you know, yes, the meta-analyses suggest that virtually all antiresorptive drugs have about a 20-25 percent reduction in non-vertebral fractures.

And that degree of reduction might be a little less in populations that have somewhat lower risk. And so that would fit the picture here, but I think that it's well within the range of non-vertebral fracture risk reduction you see across drugs, because non-vertebral fractures are difficult to prevent with just antiresorptive therapy, because their etiologies are so complex.

DR. ROSEN: So that's correct. So I think -- and maybe you can help me, Steve. I don't want to get this into a personal conversation between you and I, but when we talk about weighing risk versus benefit and we have 20 percent non-vertebral fracture risk reduction where patient specific outcomes are involved, and then you have these rare events that are not quite statistically significant or may be barely statistically significant like neoplasm, how do you balance those two events? Because I think this is actually at the crux of the problem.

We have rare events that are occurring because you're studying lots of people and you have effect sizes that are similar to the other drugs.

DR. CUMMINGS: I can speak to the benefit side and, as you know, clinically, it's important to assess the risk of an individual patient, which can be done both with bone density and other considerations. And so this ends up being a clinical judgment about the risk of the patient that's sitting in front of you based on the age, their bone density and other things and the degree that their risk is increased, the benefits from non-vertebral fractures, as well as vertebral fractures, will be an important consideration in making the decision to treat and treat with this agent.

DR. EISENBERG: And again, the rates in terms of risk are very low, absolute rates, both for SAEs, are low. And the rates for malignancy, just to be clear, are not statistically significant for any of the events we've talked about today.

DR. ROSEN: No. Well I understand, it's just that they're rare events and you'll see them in the 300,000 follow up people as well.

DR. CARSON: Dr. Collins?

DR. COLLINS: Should this drug be approved,

it'll be available for use in pre-menopausal women and children as well, theoretically, off label of course. But what do we know about safety in pregnancy and or children from the animal studies, the non-human primate studies?

DR. EISENBERG: Well, we do know that -- as was highlighted by Dr. Lacey in the embryogenesis process, that the inhibition of RANK ligand has many effects. So it certainly would not be a drug we would want a woman who's pregnant to be exposed to.

In terms of reproductive effects, there aren't any specific known effects of inhibition of RANK ligand in terms of reproductive effects. In children, we have programs for pediatric investigation.

It turns out, for example, that giant cell tumors, which are an unusual tumor, are driven almost entirely through the RANK pathway and we have some evidence that inhibition of RANK ligand is very helpful for those patients. But one has to be careful because of the effects on developing bone, not to treat pediatric populations before the FCL plates have

fused. So those would be the general concerns, and we certainly would have labeling that it should not be used in a pregnant woman.

DR. COLLINS: So this does cross the placenta I guess then.

DR. EISENBERG: We don't have data that it does, but clearly, an abundance of caution would be appropriate.

DR. CARSON: And the final question, I'd like to bring up again. I'm concerned -- I want to bring up the weight data again that we began to talk about, that in Study 216, we see no change in fractures after three years, but a significant change in bone mineral density. And then that surrogate marker for fracture becomes our primary outcome in the other studies. And although we see a definite change, we also see changes.

Do we expect still, no fracture change? And so it seems that there is a little bit of disassociation between the actual bone mineral density change and the fracture risk. And when you consider that in light of the difference between the denosumab

and placebo groups, the bone mineral density changing in that group with different body weight, I think it's somewhat concerning.

You make the point that bone mineral density changes less in the placebo groups with higher weight, and I gather that's what your explanation of is the difference.

It still concerns me that should we be considering weight in our patient -- in our sub -- when you do the subgroup analysis for weight, is that something we should be considering in which groups would benefit most by treatment?

DR. STEHMAN-BREEN: Just to clarify, the absolute changes in bone mineral density are the same across body weights. Let me highlight the consistency of effect that we've seen for new vertebral fracture year-by-year.

So this analysis was done looking at the incidence of vertebral fracture between zero and 12 months, 12 and 24 months, and 24 and 36 months. And as you can see, there is great consistency of effect when you look at new vertebral fracture. You see

similar sustainability of effect when you look at non-vertebral fracture.

In the FDA presentation, they highlighted the hip bone mineral density during that third year, There was a very small number of fractures, but there were slightly more numbers of fractures in the placebo group, but it's important to highlight that the fracture rates in the placebo group were actually declining over time.

The fracture rates in the placebo group were sustained. This suggests that it's possible that in the denosumab group, this suggests that there may be a survivorship phenomenon in the placebo group that's resulting in fracture rates that over time declined. So you have a healthier group in the placebo group over time, perhaps due to some drop out, perhaps due to fractures. So again, the lack of difference you see in the third year is primarily driven by a decline in the fracture rates in the placebo group, rather than a lack of sustained effect in the denosumab group.

Now with all of that said, the treatment by

time interaction was not different. The Kaplan-Meier curves continue to show separation at three years. So the totality of this data together suggests that we do have a sustained effect with regard to fracture over the three year period of the study.

DR. CARSON: There's no change in that third year, but yet there's a significant decrease in BMD.

DR. STEHMAN-BREEN: So it's a relative -- oh, there's no significant decrease in BMD during the third year; If we can pull up the bone mineral density slide.

You can see that bone mineral density continues to increase over the three years of the study. Now it's expected that most of the increases in bone mineral density will be seen in the first year of the study, due to mineralization. This is a phenomenon that's observed with any therapeutic for osteoporosis.

DR. CARSON: I misspoke, but what I'm saying is you see a difference in bone mineral density, but yet no difference in fracture rates.

DR. STEHMAN-BREEN: We do. We continue to

see -- if you can please put the vertebral fracture, year-by-year data up.

At the third year, we continue to see a significant -- 65 percent reduction in new vertebral fracture, which is very similar to the overall 68 percent reduction that we see over the entire three-year period.

If you look again at non-vertebral fractures, we see a very similar phenomenon where every time period, zero to 12 months, 12 to 24, 24 to 36, you see very similar levels of reduction. And if you can put the slide up, you can see that you see similar relative reductions in non-vertebral fracture risks favoring denosumab in each of those three time periods.

DR. CARSON: Could we see the hip as well?

DR. STEHMAN-BREEN: I believe we have a slide that has the incidence rates across all studies.

If you could put the slide up, across the PMO fracture study. So here you can see new vertebral fracture, non-vertebral, hip, major osteoporotic and clinical vertebral fracture.

DR. EISENBERG: And it's very clear what's happening. If you focus on hip fracture, these are the same data that were shown earlier by FDA, the rate in placebo is what's going down. And again, keep in mind the design of the study to protect placebo treated patients, because they got best standard of care, Vitamin D and calcium. You expect the higher risk patients will actually over time come out of the study, because they would have been more clinical concern. But the effect of denosumab in every study we've done, including the preclinical studies, all of the data does not change over time.

DR. CARSON: And again, I hate to harp on this, but again, you say the difference between the denosumab and placebo groups decreased with increasing body weight.

DR. STEHMAN-BREEN: Why don't I have Dr. San Martin, who is responsible for those analyses, elaborate on this further?

DR. SAN MARTIN: I'm sorry. Maybe I didn't answer the question well in the morning.

Can I have first the slide with that shows

in the X axis the weight and in the Y axis, the bone mineral density?

So you can see in the X axis different body weight and in the Y-axis change in bone mineral density. And obviously, there is no correlation between changes in bone mineral density and baseline body weight. Same is true for bodyweight PK or expression to denosumab.

So there is really no relationship between BMD changes and body weight. Now because the patient who has high body weight, tends to not lose bone mineral density that much than between denosumab and placebo may now be -- are the same when you see the patient with very low BMI and those with higher BMI, but that's not affected in this slide.

DR. CARSON: This is really not an answer to my question. I'm saying that in the 70 kilogram weight group, for example, you have a difference between your treatment and your placebo group than in -- so that says to me that women who weigh a little bit more are not going to benefit by this drug as much as women in a --

DR. SAN MARTIN: That's a good point. Let me show you this slide please.

So the third bullet point represents the changes in bone mineral density for patients with different body weight between denosumab and placebo. And as you see, the difference is smaller in this patient with higher weight at baseline. And the reason of that in part is because this is expressed in percent change, and the baseline BMD in those patients with heavy weight are higher.

So the absolute gains in bone mineral density is essentially the same, despite the baseline weight. I don't have a slide that specifically addresses your question, but we did perform that analysis, and clearly -- oh here, this is the fracture.

So I already showed you the fracture reduction, which is consistent across all body weight. But again, the bone mineral density difference is essentially due to the baseline difference in bone mineral density across different patients with different baseline weight.

DR. STEHMAN-BREEN: Just to reiterate, regardless of weight, denosumab results in a similar absolute increase in bone mineral density.

DR. SAN MARTIN: That's right.

DR. CARSON: Dr. Buzdar?

DR. BUZDAR: Yeah, one question which I wanted to ask was that if you showed the data in year one, two and three, and according to your initial reports that you have observations up to six years, the question is that after that, what happens to the difference in fracture rate? Do they start to become closer to each other? Do you have any slide to show that?

DR. EISENBERG: Well the only time -- because, again, these are -- well best standards of care, other than a biphosphonate or raloxifene treatment, it's not ethical to continue patients on long-term comparisons to no treatment, because these are patients with osteoporosis.

So the long-term data, after three years, everybody that we're following, the 4,550 patients that I highlighted in the presentation, all of those

patients will receive denosumab, and we continue to monitor those rates, but we can't compare them to placebo.

Is that what you're interested in or am I not getting it right?

DR. BUZDAR: No, that's exactly the point. Even let's say that they get crossed over from placebo to now your active drug. The question is, is there any difference? Do those differences disappear? I think it will be still important, because some of the oncology trials -- timing of initiation of therapy also makes significant difference.

Dr. STEHMAN-BREEN: So I just want to clarify, the data that we have out to six years is from our Phase 2 study, where we have a long-term follow up period, that's not a very large study, as you can imagine, now that we're out to six years. And so it's really not a study -- in addition it's not placebo controlled. And so it would be really for multiple reasons, and so, it would be, really, for multiple reasons, not possible to look at fracture rates in that study.

Now the other study that was being highlighted is the long-term extension study from our big fracture study. And again, the extension period has only been going on for a year so. When that data becomes available, Dr. Cummings as head of our Steering Committee and now our Publication Committee, is working on analyses that will allow him to do analyses that he calls virtual twin models, that will help us understand the fracture rates over time.

DR. CARSON: Okay. Thank you very much.

It's very clear that you're well familiar and the whole team knows the data. Let's now address the questions that are asked to us.

For this session, we will have time to discuss and we'll be using the new electronic voting system for this meeting.

Each of you panel members have three voting buttons on your microphone: yes, no, and abstain. Once we begin the vote, please press the button that corresponds to your vote. The final vote will then be displayed on the screen. I will read the vote from the screen into the record. Next, we will go around

the table and each individual who voted, will state their name and vote into the record as well as the reason why they voted as they did.

So let's begin with question 1A.

Is there a population of post-menopausal women with osteoporosis in which the benefit of treatment with denosumab is likely to outweigh the risks? And if you would vote now.

DR. PAZDUR: There's no discussion of this question? People don't want to discuss this before they vote. Going, going once, twice.

DR. CARSON: I think we would like to discuss -- discuss before we vote is okay. Okay.

DR. BUZDAR: I think the way the question is put, maybe we need to discuss. It's a very ambiguous question.

DR. CARSON: Why don't you begin?

DR. BUZDAR: Yeah, I think the thing is that question, if I read it, is there a subgroup in which the risk is greater than the benefit. That's what you're trying to ask?

DR. CARSON: Is there a sub -- it says -- is

there a subgroup that, right, would most likely benefit more than the risks that you've heard today? Any particular subgroup in the group of osteoporotic post-menopausal women?

DR. ROSEN: Okay. I think that you're referring to treatment, correct? Not prevention. This is directly related to treatment.

DR. CARSON: Right.

DR. ROSEN: Right.

DR. CARSON: This is post-menopausal women with osteoporosis, and would treating their osteoporosis receive more benefit than risk?

DR. NELSON: The way I would read the question is, it doesn't necessarily have to be all post-menopausal women would benefit.

Is there a group of women?

DR. CARSON: It's post-menopausal women who already have osteoporosis, are there groups already in that group that would benefit.

Dr. Emerson?

DR. EMERSON: Well I guess I'd come down on the decision. First of all, I mean I think separating

out groups, subgroups of the clinical trial, would be fraught with peril, personally. But in the large clinical trial with 8,000 women, they had a benefit, but the number needed to treat is all important to me. And, basically, numbers agree with much of the sponsors, but roughly to prevent any fracture, you'd need to treat 16.

To treat hip or vertebral fractures, it's 18. But by the time you get up to hip, it's 200. And the question there then, a lot revolves around how important the vertebral fracture is for quality of life. And my inclination, not knowing anything else but testimony on this, is that that's pretty high, as compared to going with the non-significant results, interpreting just as if they were known, the roughly 1 to 1 and a half percent difference in serious adverse events of every kind, that likely the decrease in quality of life from the fractures in this population, the sort of population they were tested was worse from the fractures than it is from the unknown risks that haven't totally been quantified.

So I guess I'm sort of down on the side of

saying, for the treatment as defined in that trial, it's looking like that group would benefit.

DR. CARSON: And that group -- the whole group.

DR. EMERSON: Is that the inclusion criteria in that whole clinical trial.

DR. CARSON: Dr. Richardson?

DR. RICHARDSON: Well, I think there's a lot of difference among these vertebral fractures though. I mean if you're talking about somebody who really crunches down their vertebra, obviously that's major event fraught with pain, a lot of morbidity. But we see a lot of guys who -- when you look at the lateral views on their chest x-rays -- they've got a little bit of loss of height anteriorly on one or two vertebra, they're totally unaware of it. And are you counting those in your vertebral fractures?

DR. EMERSON: There's no question that they were using the subclinical increase in vertebral fracture as a new vertebral fracture. So if they had that -- some level of compression they saw, if it had increased by a certain amount in some vertebra, it was

counted as a new fracture. And I'm not certain what the significance is, other than this is a group of women who already have severe osteoporosis at a level -- 24 percent have had previous fractures.

DR. CARSON: Dr. Rosen?

DR. ROSEN: Yeah, I would favor Dr. Emerson's position. I actually think for a bone active drug, this is as good as it gets for non-vertebral fractures. Even forgetting about vertebral fractures and whether they're silent or not, but remember silent vertebral fractures have an increased risk of mortality and morbidity anyways. So with numbers needed to treat less than 20, that's pretty impressive for people who suffer from osteoporosis.

And in that group, in that cohort, that's a highly effective group, multiple fractures in many cases, and very low bone density. So I certainly favor yes on this particular issue.

DR. CARSON: And would you clarify what subgroup then of post-menopausal women with osteoporosis you would favor yes to.

DR. ROSEN: So I mean I think you have to

look at the cohort. And the cohort is T-score is less than minus 2.5, the average age is over 70, and about a third of them have fractures if I remember correctly. But that's a high risk subgroup. That is the group that they designate to look at fractures, because those are the ones that are most likely to fracture.

So I think it would be very difficult to parcel out individual subgroups from that. I think for a treatment of post-menopausal established osteoporosis, it fits.

DR. CARSON: So then you're really saying the answer should be no, right? That it's the whole group --

DR. ROSEN: Well I think Dr. Nelson summarized it correctly. The way the question is phased, in a population of post-menopausal women with osteoporosis, is the benefit of treatment likely to outweigh the risk? And I would say the answer is yes to that.

DR. CARSON: Dr. Margolis?

DR. MARGOLIS: Yeah, I would agree with both

Dr. Emerson and Dr. Rosen. I would agree that based on the data from the clinical trial for the population that was studied in the clinical trial, it appears the drug is effective. I think what is very dangerous is we're going to go into that clinical trial and all of a sudden decide there's one subgroup that's better than another. The study wasn't designed to do that. As an epidemiologist, I would strongly discourage people from doing that.

If people are concerned about their risk, that really then goes to the importance of question number 6 in terms of how things are going to be viewed in the future in terms of post-marketing studies and risk discussions with physicians and patients.

DR. CARSON: Dr. Nelson?

DR. NELSON: The other thing I read into question one is, is this an effective drug and should it be out there for clinicians to be able to make a decision on individual patient -- yes, this is a severe enough case that we can use this agent. That's what I think should be used to determine the answer to question 1, so I would say yes.

DR. CARSON: Any other discussion? Okay, I'd like FDA staff to correct this if I'm wrong. We're going to ask this question, assuming that the population that we're voting for is the study population rather than subgroups within post-menopausal women. So a yes would mean that the study population or population of post-menopausal women would benefit from treatment more than they would have a risk of treatment.

So is there a population of post-menopausal women with osteoporosis in which the benefit of treatment with denosumab is likely to outweigh the risks?

So please -- we can't vote. Okay, now we can.

Now will the lights go off when our vote is registered? Okay, let's try again.

Okay. There are 15 votes. Is that correct?

Are there 15 voting members of the committee? Then the result is that unanimous, all committee members voted yes.

So let's begin with Dr. Gut. And will you

read your vote into the record and state why you voted?

Oh, you're not voting. Oh, okay.

MS. SOLONCHE: Martha Solonche, and I voted yes. There is a population of post-menopausal women with osteoporosis who will have benefit from this drug that will outweigh the risks.

DR. CARSON: Dr. Gulley?

DR. GULLEY: Yes, clearly I think that -- I voted yes, clearly that Trial 216 managed primary endpoint, and this was a clinically significant finding, too, besides being statistically significant.

DR. RICHARDSON: Ron Richardson. I voted yes with some concerns however. I'm not sure why -- that we've identified that subgroup, and I think I'm concerned about the fact that we are exposing a lot of healthy people to risks.

DR. MORTIMER: Joan Mortimer. I voted yes because the study met its primary endpoint. There was a decrease in vertebral fractures.

DR. BUZDAR: Yeah, Buzdar. I voted yes. I think overall there was significant reduction in all

fractures. Still I think the question about the safety, I still have reservation, but I think overall from the efficacy point of view, there was marked reduction and I support that.

DR. MARGOLIS: David Margolis. I voted yes, based on the results that were present from study I guess 216. However, I think the risk evaluation mitigation strategies that we'll discuss later will be very important.

DR. NELSON: I voted yes because the evidence shows that this is effective in reducing fractures in this population. And the agent, in my opinion, should be available for clinicians, then weigh the risks that have been outlined here to decide whether to use it in an individual patient.

MR. GOOZNER: I voted yes, a little bit reluctantly. To repeat what people said, it is overwhelming that this drug works for what it was designed to do, but I think because of the unknown quantity of the risks -- and we'll discuss more about this later -- I definitely think that it ought to be used almost like a second line therapy for when people

find they're intolerant or have not been effective with the other drugs that are already out there.

DR. JOHNSON: Yes, Julia Johnson. I also voted yes. I will mirror what others have said in that I have significant concerns about potential long-term effects of this medication, whether it's over suppressive on bone turnover and whether it causes immunosuppression, which can lead to infection or cancer.

I think that we need to look at this very closely, and I think if this is a unique medication and therefore beneficial to women who do not tolerate other medications that prevent fractures. But I do think we need to talk about that extensively when we talk about question 6.

DR. CARSON: Carson. I voted yes, because it decreases fracture risk in this population.

DR. EMERSON: Scott Emerson and I voted yes, because I felt that this is a patient population that was seeking treatment for their disease, and that while there are uncertainties about the long-term safety and the very rare conditions, that I felt that

the incidence of the complications of this disease in this patient population warranted a treatment.

DR. BENNETT: John Bennett. I voted yes, because of the very well done Study 216. I congratulate the company on a very well done, carefully analyzed trial.

I'd want to comment something about so-called asymptomatic vertebral fractures. I think there are patients in the intensive care unit who are ventilated who are so kyphotic that they're very difficult to ventilate. I think they're patients who have back pain that's probably due to these fractures and it's hard to know whether or not they are. But I think we've heard from some of our commentaries from the public about the pain that goes along with this. So knowing exactly how many are due to these fractures, its difficult to say, but I think that's part of the morbidity that we're trying to prevent with this drug.

DR. UZEL: Gulbu Uzel. I voted yes, because I believe, as supported by the evidence presented here today, that this drug is effective in preventing

osteoporosis in the population targeted.

DR. ROSEN: I'm Cliff Rosen. I voted yes for the reasons I stated previously and everybody else has stated since.

DR. COLLINS: Mike Collins, I voted yes. Like Cliff, for the same reasons. I would add, though, or echo anyway, the concern for careful long-term follow up and in consideration of other dosing regimens that might get the same benefit.

DR. CARSON: Okay. We have some discussion but no vote for question 1B. And that is, since we voted yes, would this population be all women with post-menopausal osteoporosis or limited to a subgroup at a high risk for fracture defined as a history of osteoporotic fracture, multiple risk factors for fracture, or women who have failed to receive benefit from or are intolerant to other osteoporosis therapies?

Dr. Rosen?

DR. ROSEN: Yeah, I could start. I mean I think that it probably is not first line therapy. I think, obviously, there are a lot of things that go

into -- cost is one thing and safety obviously is a second thing. And I do believe that there are, as we heard today, some people who cannot tolerate biphosphonates, who would be better off with a relatively simple regimen.

So I think there probably should be defined -- something in there to guide practitioners in terms of using this drug as first line or a second line and this will be guided by several factors; I think safety being one of them that all of us are concerned about.

DR. CARSON: Mr. Goozner?

MR. GOOZNER: Yes, I think the one thing that needs to be said here is that this is a first in class drug and it's a monoclonal antibody. And historically, it was very wise to rollout first in class drugs like this, especially where there's other treatments available in a rather slow fashion so that risk can emerge over time. And I think that I would change this number 2 as written to say not women who have failed "or" intolerant of other, but make that "or" into an "and".

I think this should be a drug that is used in people who are at high risk, who sort of look like the people who are in this trial and who clearly can't use the other things that are out there or who have failed on them. And that way, over a few years, we'll get a much greater experience of what the real risk profile is of the people on this drug.

DR. CARSON: Let me just comment that if we change it to an "and", we would be excluding all those who are intolerant of it, because they would not have been able to take it long enough to fail. So it has to be "or".

Dr. Margolis?

DR. MARGOLIS: Yeah, I would be very careful again about using this drug in a population of predicting how it's going to work other than the population that was tested. So unless the inclusion criteria was that somebody had failed biphosphonate therapy, it makes it very difficult to know just how successful would it be in that population. So practically, it may end up being a second line drug because of concerns about risks, but how we could

possibly know how well it would work in that population is well beyond the data presented today.

DR. COLLINS: But you know, I think if -- I'm sorry. If you're the clinician sitting there with the patient and they failed all the other options, you have -- it's as intolerant to other osteoporosis therapy. So you have to decide and you have to make a choice. So when you're there with the patient in front of you, you don't have everything you need all the time.

DR. CARSON: Dr. Johnson?

DR. JOHNSON: Yes, and I would agree with whatever everyone else has said and encourage the company to not encourage this to be a first line therapy.

DR. CARSON: Dr. Buzdar?

DR. BUZDAR: I think the thing is that if we look at number 1, which says all women with post-menopausal osteoporosis, that is not the study population which was included. So I think that will be giving a label indication beyond the study population. So it will be, I think -- I don't know

why we're even discussing about it, because there is no data in that subset of patient population.

DR. CARSON: Any other comments?

So I feel that the committee has come to a consensus that this drug -- first, the committee has voted that there is benefit to giving denosumab in a population of post-menopausal women with osteoporosis and these benefits outweigh the risk. I feel that the committee's consensus is that the drug should be limited to a high risk subgroup, high risk for fracture, with a history as tested by the data presented, with a history of osteoporotic fracture or with high risk for fracture as well as in those patients who have either failed or are intolerant of other therapeutic measures.

Dr. Rosen?

DR. ROSEN: Yeah, I just want to clarify that this group of individuals -- to design this study to show fracture efficacy, these are relatively high risk individuals. They're over 65. They have T-scores less than minus 2.5. More than a third of them have fractures, prevalent fractures. So I mean I

think we have to be careful about subgroup because I think it's very important to remember these are true osteoporotic women.

They're at high risk, their FRAX risk indicators are 7 percent for hip fracture, which is well above the 3 percent threshold. So just a reminder that this is a relatively homogeneous group of women that we deal with that have post-menopausal osteoporosis established.

DR. CARSON: Let's move on to question 2.

DR. RICHARDSON: May I ask a question first?

DR. CARSON: Sure.

DR. RICHARDSON: Based on what you're saying Dr. Rosen, are we going to specify some sort of criterion, I mean FRAX criteria for that risk stratification for this group?

DR. ROSEN: No, I don't think we should. I'm just commenting on what the demographics of this population that they studied are, but I would be very loathe to specify a FRAX indicator. That data set continually changes, and I'd be very worried about using a FRAX threshold.

DR. RICHARDSON: But what does that mean for the clinician in practice? He can look at somebody, give them the eyeball test, and say I think you're at risk and treat?

DR. ROSEN: Well, I mean, I think we tend -- I mean, as Dr. Siris said, we now have lots of indicators for establishing risk. And if you have a high risk individual, this becomes one of the potential drugs that might be utilized in that situation. And I think that's all you can say. And, of course, we have to balance risk with benefit. But I think in terms of a practitioner looking at a patient, there are now several options that they can use.

This may not be a viable option, because it's so expensive as a first line therapy, for example. But it puts into the armamentarium and I think that's all we say, that this is one of the drugs that has about the same NNT as any of the biphosphonates and is effective.

DR. RICHARDSON: Well if you're a guy in practice and you've got a patient who comes in and you

can administer this drug parenterally in your office versus handing them the script for Fosamax, what's going to happen?

DR. ROSEN: Well, I think you have to take the whole patient into consideration, what kind of insurance do they have? Do they cover it? What's their compliance history? I mean, I think -- you've heard -- and this is a huge problem in the osteoporosis field -- compliance is 25 to 40 percent after one year. So it's really essential that we try to get at therapies that people can comply with. It may not be the first line of therapy and it may be that people are failing because they're not taking the drug, but there it is. You would have another option.

DR. CARSON: Moving on to question number 2. Is there a population of post-menopausal women with low bone mineral density who do not meet the criteria for treatment of osteoporosis, in which the benefit of prevention of osteoporosis with denosumab is likely to outweigh the risks?

So basically the same question, but for prevention of osteoporosis in women who have low bone

mineral density. So they don't have osteoporosis, they have osteopenia, and is there an indication for prevention of osteoporosis?

Dr. Collins?

DR. COLLINS: I think the answer is yes, but we don't know who they are.

DR. CARSON: Dr. Emerson?

DR. EMERSON: Well I mean my answer is going to be no, but I have to change this question very slightly in the sense of there's evidence that it's likely. And this is the problem, is that I just don't think that there's evidence in this group that it was tested in 300 women, in this group were being compared.

So only half that number on the treatment arm that -- I raised my objections to the FRAX being the 10 year time frame. I can see that that's very important for the individual women to be able to look at that prognosis, but it's not clear to me that a prevention strategy is in order yet, or that a treatment strategy is in order yet. And here's where the uncertainty in some of the more serious adverse

events just means we'd -- I'd like to have more data before I'd vote yes on this.

DR. CARSON: Dr. Rosen?

DR. ROSEN: Yes. So I would just like to reinforce that the sponsor actually did the right study because your only power -- you only need 300 subjects to show a very significant effect on bone density. The problem is does the risk justify the benefit with a large population where generally numbers needed to treat are in the 2,000 range to prevent fracture? Not to change bone density, which is not a patient specific outcome, but to change quality of life.

That's where the issue comes in, and here the uncertainty around treating large numbers of people with osteopenia -- and you saw the numbers are absolutely huge -- would be an indication. And I'm quite concerned that we still don't have enough safety data at three years out to be certain that we can advocate for a prevention study at this stage.

DR. EMERSON: And so just to clarify this whole point to saying that in this group, in the

treatment group, we showed that we could increase bone mineral density and we could decrease fractures. And there's one level to say, is that proof that the bone mineral density is a surrogate. But let's look at lowering blood pressure. If you take hypertensives and lower their blood pressure, you also improve their survival. But if you take normotensives who are at high risk for eventually developing hypertension and lower their blood pressure, it doesn't obtain. And we just don't have that information. And there's certainly just a suggestion that this isn't distilled water we're giving them, that there might be more of a risk involved.

DR. CARSON: I personally think that this is where the safety really comes into play, because what we're really talking about is a bone mineral density number. I mean, it was decided, okay, two standard deviations below or a T-score of minus 2 is osteopenia and minus 2.5, it's osteoporosis. And what we're talking about is can we prevent that.

Well this drug, certainly we've seen that it does prevent bone mineral density loss. So if we're

talking about those numbers, the answer has to be yes. But then what does safety -- because that's a numbers games and that's what I kind of worry about all of these surrogate markers that we use, and especially when we don't exactly know differences between subgroups of numbers.

But when you look at the risk of osteopenia as a number for fracture and developing further, it does progress to osteoporosis and fracture. So I think there is some benefit. But then that's when safety becomes important, and I think that we have to be very conscious of what we're doing long-term with safety.

Having said that, I think it's also important that when this drug is stopped, bone mineral density does plummet. And so that means we're talking about if we believe that this group is important to treat because of this number, we're talking about long-term therapy, and we better be convinced of its safety.

DR. NELSON: My opinion would be the answer to this is no, because there is this biologic

plausibility of immunosuppression increasing risk of infections and increasing risk of cancers. And when we're dealing with a preventative approach, we really need to make sure that this isn't going to cause any harm or cause minimal harm. So my answer would be no on this.

DR. CARSON: Dr. Mortimer?

DR. MORTIMER: But I think we have to appreciate that this population is at higher risk. I mean, Dr. Siris went through the NORA study that showed us that people in this group that would be included in the study are in fact at increased risk.

But I go back to Dr. Rosen. I mean, I just don't think we know who those patients are. And if the primary endpoint for approval on an osteoporotic drug is decreased fracture rate, I think in prevention it should also be decreased fracture rate. So we don't know that.

DR. CARSON: Any other committee discussion before we vote?

Okay, we'll try to vote. Not yet. Now.

Okay everybody, would you please vote again?

Somebody isn't registering. Yes, no, or abstain. If you don't want to vote, just press abstain. Vote again.

Okay, the voting results are there were three members who voted yes and 12 that voted no. So could we go around the room, and let's start with Dr. Collins this time.

DR. COLLINS: Yeah, I voted no, and the reason being that I just don't think we know what the population of patients is that will benefit. And until we know and until we know the long-term safety, I think I have to vote no.

DR. ROSEN: I voted no, because I'm also worried about safety, I just --

DR. CARSON: Would you say your name please?

DR. ROSEN: Oh, I'm sorry. Cliff Rosen. I voted no. So I just calculated the FRAX data set for the mean value in the prevention trial that they did, 32, and the major risk of hip fracture is only 0.9, and the major osteoporotic fracture is 9 percent over 10 years.

So if you take that into consideration,

we're talking about a relatively low risk group of individuals that do have osteopenia, and I think we don't have enough information yet about long-term safety. I'm still concerned about bone suppression in this group, so I think that's why I voted no.

DR. UZEL: Gulbu Uzel. I voted no for the same reasons. I don't want to repeat it.

DR. BENNETT: Bennett. I voted yes. I guess I'm less risk adverse. I don't see a strong signal here for concern, and I believe that post-marketing surveillance the company's projected is adequate to look at this. So we won't know until we try it, and I think we should try it.

DR. CARSON: Dr. Emerson?

DR. EMERSON: Scott Emerson and I voted no, because of the issues that I discussed earlier. Basically, that I think there's a lot of uncertainty in a low risk population, that the number needed to treat is sort of too high even in the most optimistic settings.

DR. CARSON: Carson, and I voted yes, because I was convinced by the data that this drug

does prevent loss of bone mineral density and that I'm confident that post-marketing surveys and studies will allow us to assess the long-term safety, which I agree is not quite there yet.

DR. JOHNSON: Julia Johnson. I voted no for the reasons that have already been stated.

MR. GOOZNER: Merrill Goozner. I voted no for the number needed to treat the unknown risks.

DR. NELSON: Larry Nelson. I voted no because of the reasons discussed and I think it'd be important to get more data on the more severe cases before we start using this for prevention.

DR. MARGOLIS: David Margolis. I voted no. I do believe that it diminishes bone mineral loss, but I have concern about the long-term safety, and as more long-term safety data is available, would certainly reconsider the vote.

DR. BUZDAR: Yes, Buzdar. I voted no. The reason being that here we expose a lot of patients, and still the safety data is, I would say, preliminary, and we need more safety data before we start to use this as a preventative agent.

DR. MORTIMER: Joan Mortimer. No, and for all the aforementioned reasons.

DR. RICHARDSON: Ron Richardson. I voted no for the same reason Joan did.

DR. GULLEY: James Gulley. I voted yes, because I thought that the trial met its primary endpoint and I thought that the pharmacovigilance plans that were laid out were good. I thought there may be a signal of some safety importance, but that signal may also be explained just by chance.

MS. SOLONCHE: Martha Solonche. I voted no due to safety concerns.

DR. CARSON: Okay. The committee voted no to this question that there is not a population of post-menopausal women with low bone density who meet the criteria for prevention of osteoporosis with denosumab that is likely to outweigh the risk. And it seems the consensus of the committee feels that this treatment, although it may be effective, is related to unknown risks, which may not make the benefit of prevention worthwhile.

And Dr. Rosen?

DR. ROSEN: I'd just like to amplify on what Dr. Collins said, and that is that we don't know who these people are with osteopenia that are going to go on to fracture. We're not even sure we know who those people are who are going to lose bone mass prospectively. And so that represents a dilemma. And if we knew and could identify people who are rapid losers and also more susceptible to fracture -- but that's been the dilemma in this field for awhile, is trying to identify people with T-scores of minus 1.5 or minus 1.6 who may go on to lose significant bone and fracture in the next five years. And we need more information on trying to identify that subgroup.

Currently, I don't think the markers really give us that kind of insight. So there may be a subgroup population. I'm just not sure we can identify it at this stage.

DR. CARSON: Okay, let's move on to question 3. Is a favorable risk benefit ratio demonstrated for denosumab for the treatment of bone loss associated with hormone ablation therapy in women with breast cancer receiving aromatase inhibitors?

Dr. Buzdar?

DR. BUZDAR: I think the thing over here, I have significant concern for two reasons. One is that there is a trend towards even higher incidence of breast cancer. Second, patients who are getting aromatase inhibitor therapy and were treated, there is slightly increased risk of the recurrence, which was not the endpoint, but there was at least a hint of that.

So here other bone strengthening drugs like biphosphonates, when they have been very evaluated in these subset of patients, there is even suggestive evidence of all sites recurrences are fewer. Over here, actually it is somewhat other way around.

So I have serious reservation in this subset of patients until we see more data. And the drug company has to provide the data where recurrence has to be an endpoint where they need to look at it.

You cannot just ignore that a reoccurrence is not an endpoint, which we are interested, because if the drug is having an adverse event and there are more recurrences, there are other therapies which may

be having otherwise lower risk of recurrence. This is not only in the bone but in the other sites.

DR. CARSON: Dr. Johnson?

DR. JOHNSON: Yeah, my concern with this question is that they really, at least in my mind, didn't look at treatment. They had a relatively small population base. They had relatively normal T-scores. And so I'm not sure that they've really looked at prevention effectively for this treatment. It was really more of a prevention study just looking at bone density. So I'm not sure they really address the issue of treatment.

DR. CARSON: Dr. Mortimer?

DR. MORTIMER: I'm going to sort of echo what Dr. Buzdar said, but to the data using biphosphonates in women who are on aromatase inhibitors did show an increase in bone mineral density in both hip and spine. However, that didn't not translate to a decrease in hip fractures, because then these patients stopped the drug. And what's kept the biphosphonate in breast cancer on endocrine therapy alive is the decreased risk of breast cancer

incidence. So I don't think changing bone density in this population is really that important an endpoint.

DR. CARSON: Dr. Emerson?

DR. EMERSON: And I would just concur and just add in that the standard that when you're trying to treat, basically what is a sign or symptom arising from cancer treatments, and not take into account the effect on the cancer therapy, I think that's always a bad thing to do. And this is just a great uncertainty in my mind, and I just think that that has to be verified that that's not a problem here.

The other point I'll say is that if I were going to extrapolate from one population or another -- because if we have no data on the fractures in this population, we have it either in the post-menopausal osteoporosis or we have it in the prostate cancer. And my tendency would probably be to extrapolate more from the prostate cancer in terms of the timing of the treatment and the external thing, and that basically there's not that much evidence in the prostate cancer; again, based on a number needed to treat that we're doing as much. And so I'm

extrapolating wildly there, but I just don't see the evidence. So it's not demonstrated.

DR. CARSON: Dr. Rosen?

DR. ROSEN: I just have a question, because I'm still a little confused. In the breast -- maybe Dr. Mortimer can help us on this.

So are you saying that biphosphonated treated women on aromatase inhibitors have a reduced risk of recurrent breast cancer? Is that true for oral biphosphonates?

DR. MORTIMER: That's true for IV biphosphonates.

DR. ROSEN: IV biphosphonates only.

DR. MORTIMER: And it's true with a decrease in cancer specific events, and that's also -- yes, there are a variety of instances where the biphosphonates actually look to have anti-cancer effects but --

DR. ROSEN: Right. But the only one that's been shown has been zoledronic acid.

Is that correct?

DR. MORTIMER: That's correct.

DR. CARSON: Mr. Goozner?

MR. GOOZNER: Yeah, actually I wanted to chime in on this point, because it was made -- the presentation was made to us several times that there was no drug, FDA approved drug, for people with cancer. This actually goes to the prostate cancer thing. And yet, when I went to the medical literature after what had been submitted to us, there was like 600 references to the use of biphosphonates and other drugs for bone loss in both prostate cancer and in breast cancer. And so I won't pull out of the references here.

So I was rather surprised by the lack of discussion at all on that point, both in the presentations this morning -- and for that reason I feel like -- we had a lost -- somebody had a lost opportunity here to find out more about how this drug might have compared to some other drugs that are already out there that are being used in cancer patients, and we were given no data and no commentary about it all.

So in all of the next questions, I feel like

I know how I'm going to vote.

DR. CARSON: Dr. Mortimer?

DR. MORTIMER: But the claim was approved for those indications and they are not -- but still they're being used off label.

DR. ROSEN: Let's hear this again. So there is an approval for zoledronic acid. There is not an approved --

DR. MORTIMER: No.

DR. ROSEN: So they're not incorrect in stating there are no approved drugs for the treatment of --

DR. MORTIMER: They're absolutely correct, but there are drugs that are being used in this setting that are being used off label and are being covered by insurance.

MR. GOOZNER: This is Merrill Goozner. Let me underscore that I was very curious about that and so I went to the literature. I got no less than 691 references, okay, on a PubMed search that looked at bone loss, cancer and biphosphonates.

DR. ROSEN: I understand. I'm just trying

to appreciate from the sponsor's point of view what they were trying to do and how they got their guidance in terms of this. So the concept was could they prevent bone loss in these individuals on aromatase inhibitors in breast cancer, correct? And if that's correct, then they did fulfill what they were asked to do.

DR. BUZDAR: Yeah, but I think the thing is that bone loss is not the major thing. The patients already have a fatal disease, breast cancer. They are getting aromatase inhibitor to prevent recurrence and there are a number of other options to reverse the bone loss in these patients, which are at least having no adverse outcome on the disease process itself. Over here you have a therapy which has been evaluated in a limited patient population, which may have -- at least we can say may have adverse outcome. So I think we have to be cautious.

DR. CARSON: I think it's important to remember that there is a lot of data, certainly on the Internet, certainly in PubMed, that are associated with a lot of different treatments. But our mission

here today is really to look at the information that we have at hand about one particular treatment and not really consider it among options, but rather consider it as does this drug have a favorable risk benefit ratio itself? Not compared to anything else, but rather does it have a favorable risk benefit ratio.

DR. EMERSON: And just to make the distinction, though, I like the way this question was worded, have they demonstrated a favorable risk? So it's not the question of does it have one but also do we have that demonstrated?

DR. CARSON: Isn't that the same?

DR. EMERSON: No. There can be a favorable risk benefit ratio that has been demonstrated. There can be one that's favorable that has not been demonstrated.

DR. CARSON: Well, that's true.

DR. EMERSON: Or that it could have been demonstrated that there isn't one. Somebody was complaining about double negatives, but that's my life.

DR. CARSON: Any other discussion?

DR. ROSEN: I hate to prolong this, but I just need some reassurance about the data in this particular trial about progression of malignancy in the breast cancer trial. So can somebody reinforce or reiterate for me, or let's look a the slides again?

Was there a statistically significant increase in cancer risk or --

DR. EMERSON: I believe we don't have any data on this trial. Where we did have data was in the PMO treatment study. There were six patients who progressed in that study who'd had that. So that was in the other study. It was not in this one, yes.

DR. ROSEN: Any statistical data that there is progression of disease in this study?

DR. CARSON: I think this is a very important point. And I want to ask the sponsor if we can quickly just come to the point and show us any data that you have regarding the progression of --

Do you have a slide that you can show us?

DR. DANSEY: We do.

DR. BUZDAR: Key thing will be to see number of recurrences on this subset.

DR. DANSEY: So as you are aware, this is a bone loss trial. It was set up specifically in women with osteopenia to measure outcomes from BMD. And we did as part of the due diligence for collecting adverse events, track the outcomes. Now bear in mind this is a low risk population, essentially is cancer survivors. They've completed the adjuvant therapy, and so the risk of progression is low. So when we review the information at a clinical level, we were able to determine that there were four subjects on denosumab and three subjects on placebo during the treatment phase for two years in which the denosumab was administered that we have clear evidence of the development of metastatic disease.

Then in the off treatment, that is the two year follow up, which is not yet complete, we see two subjects denosumab and two on placebo. There was only one new cancer, which was a gastric cancer. It was on the placebo.

DR. CARSON: So this two years on the drug and then 120 days after discontinuation.

DR. DANSEY: The term 120 days --

essentially it's a cut off data during that two year period. So it's not the complete two years, but it's a substantial amount of the information. We provided that information to the agency for follow up for safety information.

DR. CARSON: Okay.

DR. GULLEY: And how does this differ --

DR. CARSON: Thank you. I'm sorry.

Dr. Gulley?

DR. GULLEY: How does this differ with what the FDA presented which was --

DR. COLLINS: Right. Slide 74.

DR. GULLEY: Yeah.

DR. COLLINS: Slide 74.

DR. GULLEY: Yeah, they had nine on denosumab and five on placebo.

DR. CARSON: We'll get that.

Can we get FDA Slide 74 up?

DR. ROSEN: This is just in the 135 Study is all we're talking about in this case.

DR. CARSON: Whose slide is this?

Dr. Kehoe, is this your slide?

Oh. Is this the slide you wanted Dr. Gulley? This isn't the slide you wanted is it? There it is.

DR. COLLINS: So does this mean -- this slide, in Trial 135, this talks about imbalance in metastatic events. So these were breast cancers that were non-metastatic to start with but progressed to metastatic disease in the course of the study.

Is that what this represents?

DR. DEMKO: Yes. And also what I did was drill down, and even if it didn't say metastasis as the first word in the event, it could have said breast cancer metastatic, breast cancer progression, and metastasis. And that's how I counted the numbers, which is why they're somewhat higher than the sponsors numbers.

DR. JOHNSON: Is this on both the prostate and the breast cancer combined?

DR. DEMKO: The first one is Trial 135, the breast trial.

DR. JOHNSON: Oh, I see. Okay, sorry.

DR. DEMKO: And it's five in placebo and

nine for denosumab, and then Trial 138, the prostate trial is the second line.

DR. CARSON: Dr. Emerson?

DR. EMERSON: And not being prejudiced by too much knowledge on the subject, but both breast cancer and prostate cancer metastasize readily to the bone, due to characteristics of those sorts of cancers. And so it is just this thing of -- there is a question to answer here and it just hasn't been answered yet.

I, in my heart of hearts, sincerely hope that actually what the sponsor is hoping for is that actually this is protective against bone metastases. I hope that that's true. It just hasn't shown up and I might put a little bit of money on it, but not very much.

DR. BUZDAR: Yeah, but the data which the FDA slide shows, it's the other way around; numerically, if the numbers are in the wrong direction.

DR. ROSEN: If we could get some clarification on it.

DR. CARSON: I'm sorry.

Dr. Pazdur?

DR. PAZDUR: I'd like to just make a comment here. I think all you can say here is that these are descriptive. Okay? Somebody's asking are these statistically significant? It's impossible. These studies were not designed to put a p-value on these numbers here. They were not a hypothesis that was being tested.

Here again, you see what you get. And Aman is correct that you have a difference here, and unfortunately it's in favor -- or against, rather, the tested drug. The other information regarding progression events, I would urge a great deal of caution of interpreting any progression events unless we were very confident that these patients were assessed at the same time.

We have had numerous discussions on our Oncology Committee about time to progression and progression free survival, which is a very soft endpoint. And if this endpoint wasn't even stipulated as how frequently patients were being assessed, it's a

very muddy endpoint to be making any comments. So in essence, all you could say is, important signal; needs more data.

DR. CARSON: Any other comments, questions by the committee?

Okay, so let's vote on question 3A. Is a favorable risk benefit ratio demonstrated for denosumab for the treatment of bone lose associated with hormone ablation therapy in women with breast cancer receiving aromatase inhibitors? And now our favorite part, we get to vote electronically.

Okay. We got it.

The two members of the committee voted yes, and 13 voted no. So let's go back to this side and begin with your name and vote.

MS. SOLONCHE: Martha Solonche. I voted no because I have concerns about the development of new neoplasms and recurrence. And I say that as a three-time cancer survivor. And I'm also concerned about the risk of multiple adverse effects.

DR. GULLEY: James Gulley. I voted no, because most of the data did not look at treatment for

this group of patients.

DR. RICHARDSON: Ron Richardson. I voted no, and I don't know whether to invoke Dr. Emerson or Bill Clinton, but I was hung up on the word "demonstrated".

DR. MORTIMER: I voted no, because an increase in T-score didn't translate to anything meaningful from a risk standpoint and weighing that against the potential risks is worrisome.

DR. CARSON: Would you say your name, and repeat your vote, please?

DR. MORTIMER: Oh, sorry. Joan Mortimer. No.

DR. BUZDAR: Buzdar. I voted no because of the safety concern in this subset of patients and slightly in the wrong direction, i.e., the increased risk of the recurrence in small number of patients which have been studied. So we don't know how safe is this molecule to be given to patients with established cancer, even though it might be a micrometastatic setting.

DR. MARGOLIS: David Margolis. I was one of

the few who voted yes. I think that it probably does prevent bone loss in a disease that for many is becoming more and more of a chronic disease, but I do agree that there are some concerns about long-term safety. I'm just not sure that the current study actually shows that there's a problem with recurrence of breast cancer.

DR. NELSON: Larry Nelson. I voted no, because of concerns about need for more data about how this affects their primary disease.

MR. GOOZNER: I'm Merrill Goozner. I voted no. To approve this drug for use in this patient population would put it at the head of the class, when there's a standard of care that apparently -- or close to a standard of care that's already out there, where we don't really have good information about, much less have good information about the real risks of this drug. So I think that that would be a terrible, terrible mistake.

DR. JOHNSON: Julia Johnson. I voted no. I thought that this study was well done to show a decrease in bone loss but didn't really show the

prevention that they were looking for. I'm sorry -- the treatment they were looking for.

DR. CARSON: Carson. I voted no because I'm concerned about the data about long-term safety of recurrences and metastasis in a disease that goes to bone and what effect remodeling might have on that.

DR. EMERSON: Scott Emerson. I voted no for the reasons I've stated earlier.

DR. BENNETT: John Bennett. I voted no because I'm concerned about the progression of the primary disease, which would be a lot worse than having soft bones.

DR. UZEL: Gulbu Uzel. I voted yes, because I think imbalance is not the same thing as statistical significance. I acknowledge concerns, but that was my vote.

DR. ROSEN: No. I voted no, but I'd like to have an editorial comment. And that is that I'm afraid that the guidance provided to the sponsor was not appropriate to the question that was asked. This is powered for bone density. It's not powered for this kind of outcome that we're looking for. So they

did the study right. They showed an effect. They didn't have the power to do it. But that to me is a breakdown between the sponsor and the FDA.

DR. COLLINS: Collins. I voted no and echo Dr. Rosen's response.

DR. CARSON: Dr. Rosen, could you state your name and your vote.

DR. ROSEN: And take back the statement too?

DR. CARSON: I think we heard it.

DR. ROSEN: Cliff Rosen, and I voted no.

DR. CARSON: Okay. Any other statements before I summarize?

DR. ROSEN: I think I've got myself in enough trouble.

DR. CARSON: Okay. To summarize, the committee has voted no against a favorable risk benefit ratio demonstrated for the drug in the prevention of bone loss associated with hormone ablation therapy in women with breast cancer. I'm sorry. Let me -- I made a mistake.

It's no against a favorable risk benefit ratio demonstrated for denosumab for the treatment of

bone loss associated with hormone ablation therapy in women with breast cancer receiving aromatase inhibitors. The consensus seems to be that the concern for long-term safety data in these women was not demonstrated in the information provided.

Let's move on to question 3B. And now, again, is a favorable risk benefit ratio demonstrated for denosumab for prevention of bone loss associated with hormone ablation therapy in women with breast cancer receiving aromatase inhibitors. And this is again, the same question, but prevention rather than treatment. Let's begin the discussion.

Dr. Mortimer?

DR. MORTIMER: So I guess I'd have to say yes, it does increase your bone density. What's hanging out there is does it matter, and I'd say it doesn't matter.

DR. CARSON: Yes?

DR. BUZDAR: Yeah, I think the question is exactly the same. Over here the question you have to keep in mind is the risk benefit ratio, they have not established and shown that it is safe, because there

are fewer additional recurrences in the patients who got the antibody treatment compared to the patients who got placebo. So even though you change the bone density -- but I think you may be having an adverse outcome, and I would say that it will be wrong to support that statement.

DR. CARSON: Any other comments? Many of the issues that we've heard before are still the same; demonstrated, and then can you choose the patients who have osteopenia who would be provided benefit for osteoporosis in fracture. And they remain the same in this question.

Any other discussion? Okay, let's vote.

I'm told the flashing lights do not go off, but you do need to press yes, no or abstain.

How'd we do? Oh, at least the committee's getting better. There was 14 of the committee voted against and there was one abstention. So let's begin with Dr. Collins.

DR. COLLINS: Well, I mean I think if one voted no to 3A and you extend the logic, you have to vote no to 3B and again offer the same reasons.

DR. ROSEN: Dr. Rosen. I agree with Dr. Collins. I voted no.

DR. UZEL: Dr. Uzel. This is the same reason that I voted abstain, because I voted yes for the first reason, first question.

DR. BENNETT: Dr. Bennett. I agree with Dr. Collins and I voted no.

DR. EMERSON: Scott Emerson and I agree with the chorus over to my left.

DR. CARSON: Carson, and I voted no for the same reason I voted no for the last question.

DR. JOHNSON: Julia Johnson and I voted no.

MR. GOOZNER: Merrill Goozner. I voted no.

DR. NELSON: Larry Nelson and I voted no for the same reason as before.

DR. MARGOLIS: David Margolis. I voted no. I think treatment and prevention are different and the risks aren't well enough stated.

DR. BUZDAR: Buzdar. I vote no. I think the sponsor needs to show that it has a better therapeutic index and has more favorable profile in this subset of patient population. And up to now, the

data is not in support of it.

DR. MORTIMER: Joan Mortimer. I voted no.

DR. RICHARDSON: Ron Richardson. I voted no.

DR. GULLEY: James Gulley. I voted no.

MS. SOLONCHE: Martha Solonche. I voted no.

DR. CARSON: Okay. Let's move on to question 4. Is a favorable risk benefit ratio demonstrated for denosumab for the treatment of bone loss associated with hormone ablation therapy in men with prostate cancer receiving androgen deprivation therapy? So essentially the same question as 3 but for men with prostate cancer.

Let's open the discussion.

Dr. Collins?

DR. COLLINS: Could we have the opportunity to briefly review the data again as we did before with the breast cancer? Both here, though; not only, slide 74 from the FDA but also Amgen's slides in terms of fracture prevention as well.

DR. CARSON: For this group?

DR. COLLINS: Yes.

DR. CARSON: Okay. Would you share those with us again? And while you're doing that, maybe Dr. Emerson, are you able to ask yours?

DR. EMERSON: Yes, in terms of looking at that and the number needed to treat in this group, that if we take that face value, I computed that it would be about 50 in order to prevent one fracture of any type in this population, a much lower rate of fractures in this particular population with, again, my fears that saying this is a cancer that is prone to bone activity and we haven't really looked at what it's doing. And so all my same disclaimers about the breast, but I just don't think it's been demonstrated.

DR. CARSON: Okay, please go ahead.

DR. SMITH: If you'd bear with me for just a moment, I think it's worth pointing out that there's been no prior large fracture prevention study in men in any setting. And when we designed this trial in 2004, we were faced with the dilemma of identifying a patient population at somewhat increased risk for fracture, so that we could demonstrate a benefit but really having no prior large database on which to base

the patient selection.

I believe the data that we presented shows that we were successful and that we've demonstrated robust benefit on BMD, and as you show here, a reduction in vertebral fractures, that it was of comparable relative magnitude to that shown in the large PMO study.

The number needed to treat, of course, is very dependent upon the baseline risk for fracture. And as I'd indicated, there was no firm basis on which to identify patients in the past. And there's really no other therapeutic to compare these results to, because there's never been a large fracture prevention study done in men in any setting, and certainly not done in hypogonadal men.

The studies that were eluded to in androgen deprivation therapy or in HALT in other settings are all very small studies typically involving a dozen patients to, at most, 200, most with one year of follow up. This is the largest study completed to date with 1,500 patients approximately and three years of follow up. And it's nice to see, I think, that the

fracture benefit seen is very comparable to that what we're seeing in the treatment study in PMO.

DR. CARSON: Okay. So this is the decrease in new vertebral fractures.

DR. SMITH: Correct.

DR. CARSON: And Dr. Johnson?

DR. JOHNSON: Did you look at non-vertebral fractures?

DR. SMITH: We do have that data. And as the endocrinologists on the committee could speak to much better than I can, to show BMD benefit requires dozens to perhaps a few hundred patients. To show a reduction in vertebral fractures requires perhaps a few thousand patient years of follow up as we had in this study. To show a significant reduction in non-vertebral fractures or any clinical fractures, we believe would require probably many more thousands of patient years of follow up.

DR. CARSON: Do you have the data for non-vertebral fractures? Can we see that?

DR. SMITH: Well so this is any -- this is any fracture outcome showing a trend in favor of

denosumab. It didn't reach statistical significance, and then you see the endpoint of multiple vertebral fractures at any site showing a reduction in benefit of denosumab.

DR. CARSON: And then I believe there was also a --

Dr. Collins, you also wanted to see the metastatic cancer risk.

Do you have that as well? No?

DR. COLLINS: Well it was the same FDA slide we saw before. If we could see it again.

DR. SMITH: Yeah, so it's that same FDA slide that was shown earlier in the discussion, the AI treated patients.

DR. CARSON: Oh, Slide 64?

DR. SMITH: I believe Dr. Pazdur made a very important comment in that ascertainment of outcomes like disease progression by AEs are very problematic and potentially unreliable because of the issue of -- there's no pre-specified time of ascertainment of these types of outcomes.

So if I could have -- so as you can see,

there was a numerical imbalance that was in favor of placebo in this, but we also very carefully looked at in a pre-specified manner at specified time points, a disease progression by three metrics -- PSA progression, bone scan progression and then we have overall survival data.

So this PSA data that you'll see was all centrally measured. It was done at six month intervals. There was very careful ascertainment of the PSA outcome, and as I described earlier, at each of the time points, there is no suggestion of worse cancer progression by PSA criteria that would suggest a detrimental effect of denosumab.

Now we also looked at bone scan progression, and, again, this has the strength of being done at pre-specified time points, including end of study. And here you see that there's really no deleterious effect of denosumab in terms of bone scan progression with really overlapping curves.

Further supporting the safety of denosumab in this patient population is the overall survival data, showing that there's no deleterious effect of

denosumab in overall survival.

So I think by several important metrics, PSA progression, bone state progression and overall survival, that there's no suggestion, there's no hint that denosumab has any deleterious effect on cancer control. And as I'd alluded to earlier, we actually believe that denosumab may delay or prevent disease progression. And there's an ongoing trial, it's fully approved, and that study will look at the primary outcome of bone disease progression or death as the primary outcome. The study is fully approved and we expect to have that data relatively soon.

DR. COLLINS: So what's the difference in dose between the study you just spoke of and this?

DR. SMITH: Yes. So this of course was an osteoporosis study and we have the disease progression data as I presented. The dose and schedule in the metastasis prevention study, the 147 Trial is 12 times higher. So it's the same dose and schedule as is being used in the treatment of metastatic bone disease.

DR. COLLINS: So will we really be able to

extend those data to this population, you think?

DR. SMITH: Well I think these are the data that we can speak to now about the theoretical concern that denosumab would worsen cancer progression, right? So I think that stands for itself. The hypothesis we're testing in the other trial is actually that it'll have a favorable effect.

Now if in fact there was a deleterious effect, we'd of course expect the signal to be really quite substantial in a treatment at 12 times the dosing schedule.

DR. CARSON: Yeah, unfortunately we do have to limit our discussion to the data that was presented in the studies that are completed.

DR. COLLINS: Right. But then there seems to be a discrepancy between your bone scan data and the FDA data in terms of -- how did you assess metastatic disease in this prostate cancer population if it wasn't by bone scan?

DR. SMITH: Well I believe that -- I'll let FDA speak for themselves, but the data for adverse events is ascertained just as their investigator

reports using MedRA terms. And as Dr. Pazdur nicely pointed out, there are limitations to such data. In fact, when we drilled down into this data, at least a third of the so-called disease progression, adverse events had no corresponding PSA progression, which as a medical oncologist who only takes care of men with prostate cancer is really kind of an untenable category that there'd be disease progression with no corresponding PSA progression.

So I think it just points out to the fact that there's limits to the reliability of cancer progression as ascertained by adverse event data.

DR. PAZDUR: And let Dr. Pazdur point out one more time these are exploratory analyses, and I think we have to be very cautious in making and definitive conclusions on this. Here again, I think more data is necessary here, really, to be making exploratory and descriptive analyses.

DR. COLLINS: But I think since we have to decide today, and given the data we have to work with, I find the sponsor's data in regard to this probably stronger and generally comforting.

DR. CARSON: Dr. Rosen?

DR. ROSEN: Thank you. I'd like to explore with the sponsor, if it's okay, the vertebral fracture -- I mean the total fracture incidence in this population with prostatic cancer patients.

So the baseline characteristics were 23 percent of these men had prevalent vertebral fractures and you have a clear trend towards reduction in total fractures and a reduction in new vertebral fractures. The placebo rate of fractures was 7 percent.

Is that higher than the rate in, let's say, Mr. Osser (ph), for a 75-year-old man with a 7 to 7 and a half percent fracture rate per year?

What I'm trying to get at is whether this group of men is at high risk for a fracture, either vertebral fracture or other fracture. So how does the prevalence of fracture in this population correspond to prevalence in a normal male population of 75 years of age without prostate cancer?

DR. CARSON: Dr. Mortimer?

DR. MORTIMER: I mean there is no literature

that demonstrates that men with prostate cancer have lower bone densities than do normal men in the population without prostate cancer.

DR. ROSEN: Right. I guess what I'm trying to get at is whether or not this is a -- there's a high rate of fracture -- a higher rate of fractures in men with prostate cancer that have -- 25 percent of them have prevalent vertebral fractures. So this represents a high risk -- I guess what I'm trying to say is, is this a high risk group of individuals who require interventions?

DR. SMITH: I believe so for several reasons. I mean, as you pointed out, this patient population is at substantially increased risk. About a quarter of the patients had prevalent vertebral fractures, which interestingly enough is not too dissimilar from the 216 PMO population, right? I think it was pointed out that the T-scores were relatively normal, but I think it's also worth noting the usual limitations of screening for osteoporosis in older men, particularly with limitations of spinal BMD.

But I'd also like to point out a couple of other things, that 80 percent of the men had either osteopenia or osteoporosis, at at least one measured skeletal site. So they're a relatively ill population from a fracture risk perspective.

The other point is that the impact of the androgen deprivation therapy on fracture risk is largely explained by bone, but there are other issues, including muscle loss, obesity and frailty, which we believe placed them at particularly high risk for fracture.

DR. ROSEN: Yeah, I'm not interested in bone density. I'm interested in fracture risk, and it sounds like due to androgen deprivation, maybe Steve can help us on that versus normal males.

DR. CUMMINGS: Seven percent vertebral fracture risk over the course of two years is somewhat higher than seen in Mr. Osser, other male studies. You're exactly right, Cliff. But that's in part because these men are losing bone more rapidly in the absence of not only testosterone but estrogen. That's, you know, the controls preservation of bone.

So yes, they're at somewhat higher risk for the number of fractures.

DR. ROSEN: So I guess one of things too -- so when did these men enter the study in terms of castration. Had they been castrated for a period of time? Did they start treatment when they started androgen deprivation therapy? And also, what's the expected length of androgen deprivation therapy? Are we talking about a group who are only going to treat for three years or a group who are going to treat for 10 years, when we don't know the ten year risk -- that sort of thing.

DR. SMITH: Well again, we know what we know, and this is the first large fracture prevention study in men. It was required that the patients would go on androgen deprivation therapy with the intention of remaining on therapy for the duration of the trial. So most of these are going to be salvaged patients, patients who, by the way, do very well, which is why we're concerned about these issues related to survivorship.

The median time on androgen deprivation

therapy at study entry was approximately three years in both groups, so these were mostly patients receiving long-term treatment.

DR. CARSON: Dr. Buzdar --

Oh, I'm sorry. Do you want to finish about this?

DR. ROSEN: Not knowing the prostate cancer field well, these people were on androgen deprivation therapy for three years when they entered and will they be on androgen deprivation therapy for a lifetime or --

DR. SMITH: Yes, so there is different contexts for which the therapy is used, but a very common scenario is for patients with recurrent disease, which represented most of these patients, it's going to a lifelong androgen deprivation therapy.

DR. CARSON: Thank you.

Dr. Buzdar?

DR. BUZDAR: Yeah, I have never treated prostate cancer in my life, but the thing which I want to get some clarification on is that looking at the FDA interpretation of the same data, there is almost

50 percent increase in the risk of progression of the disease.

Question is who to believe. Is the sponsor more accurate than FDA more accurate over here? Because 40 events versus 60 events, which are disease progression on the antibody therapy.

DR. ROSEN: Well my interpretation, as I said before, is that the sponsor's data strike me as stronger. If it's not there on bone scan, it's probably not there.

DR. CARSON: Do you want to comment on just the discrepancy of the -- where the difference is.

DR. DEMKO: It's the same situation. It's with MedRA, and when you drill down to the lowest level, that's not a verbatim term, you can see terms such as metastasis versus prostate metastasis versus prostate progression, and I included those in the numbers.

DR. CARSON: Is that clear?

Okay.

Dr. Mortimer?

DR. MORTIMER: Again, the other issue of

drugs approved for -- I mean these -- in the standard of care presently ongoing, these men would not be untreated. So the fact that they have low bone density, they would again be treated with an IV biphosphonate.

DR. ROSEN: I don't know that that's the case. There is no standard of care in the treatment of these guys. We just went through this whole group with our prostate cancer treatment at the NIH, and it's really -- you're hard-pressed to find anything that resembles a standard of care.

DR. CARSON: Well again, let me remind you that this is not a comparison trial or it's really limited to the data that we have on hand rather than comparing it head on head to another drug.

Okay. Any other panel questions, discussions, comments?

Dr. Rosen?

DR. ROSEN: Again, I have to come back to the MedRA analysis, and we really need some clarification on what MedRA's telling us, because we're getting this contrasting story, and I still

don't quite understand.

When you say you drill down, what are you looking at? Are you looking at what's recorded or are you looking at case reports? So these are adverse events that the sponsor has submitted?

DR. DEMKO: This is the sponsor's data and it's grouped according to system organ class, which is one of the levels of the MedRA hierarchy along with preferred term, which is a lower level of the MedRA hierarchy. And under the neoplasms class, there is an entire listing of reported terms that are reported by the investigator that are then coded by the sponsor, taking their verbatim term to a lower level term that then turns into all the different levels of the hierarchy automatically.

In some cases, I did go back where they were available and looked at the case report forms or any narratives that were available to try to confirm that these were indeed cases of metastasis. However, I did not look at every single case.

DR. CARSON: Any other --

Yes, Dr. Margolis?

DR. MARGOLIS: To maybe muddy it more, having served on numerous data safety monitoring boards where you constantly get report surveys, the MedRA data, that you then have to check with SAE reports and case report forms. You know MedRA tends to be what somebody checks a box on or uses some descriptor. They don't necessarily correspond to what you find out when you really look carefully.

It's a very different assessment and it's not fair to say it's the same data, which a few people have implied, as if it were a primary outcome, if you drawing a blood test, taking an x-ray, measuring something as part of the normal protocol. It's a different assessment.

DR. CARSON: Dr. Richardson?

DR. RICHARDSON: I got a chance to invoke Dr. Emerson, Bill Clinton; now I get a chance to invoke Dr. Pazdur in saying that we can't read too much into this. I mean one question is just how does this group of prostate cancer patients fit with the practice in the States. Fifty percent of these people had hormonal treatment as their primary therapy. Only

25 percent had surgery, 25 percent had radiation, the rest were treated hormonally.

I'm surprised they could find this number of patients with a PSA less than five treated on hormonal treatment to get into this study. So I think there are some real limitations as to how we're looking at this group and what the biology of this group is versus the folks that are out there walking on Main Street.

DR. SMITH: May I comment?

DR. RICHARDSON: Please.

DR. SMITH: So I'm a medical oncologist, prostate medical oncologist. My practice is entirely prostate cancer. Androgen deprivation therapy of course is the mainstay of treatment for locally advanced as well as metastatic disease. My practice is full of prostate cancer survivors who presented with locally advanced non-metastatic disease who are long-term PSA remission patients. So these are patients who represent a large proportion of the nearly six-or-seven-hundred-thousand men on current androgen deprivation therapy. So this a very large

population of survivors.

DR. CARSON: Thank you very much for your comments.

DR. RICHARDSON: I see predominantly prostate cancer myself, and I would say that my population is substantially different. They have to be sick enough to get there.

DR. CARSON: Dr. Gulley, did you --

DR. GULLEY: Just back to the -- I think the difference between the MedRA analysis and the sponsor's analysis, I think clearly the prospectively designed and analyzed endpoints that were presented by the sponsor, I mean I would agree with Dr. Collins, that that's what we should be looking at, not at what may or not have eventually happened and with the cases in the MedRA.

DR. CARSON: Any other comments or summary statements? I'm afraid that we don't -- thank you.

Are there any other panel comments?

Okay. Are we ready to vote? Our favorite thing.

Is a favorable risk benefit ratio demonstrated for denosumab for the treatment of bone

loss associated with hormone ablation therapy in men with prostate cancer receiving androgen deprivation therapy? We do have one less voting member.

Okay. The nine committee members voted yes, four voted no, and one abstained.

So shall we go back to Ms. Solonche?

MS. SOLONCHE: Martha Solonche. I abstained.

DR. GULLEY: James Gulley. I voted yes. I think that the data set here was bigger and there's the availability of the secondary endpoint with the improvement in fracture risk. I think that that helped with assessing the risk versus benefit, and I thought there was a clear benefit here.

DR. RICHARDSON: Ron Richardson. I voted no, mainly because I think at this point in time, the risks I think in this group haven't been completely elucidated. I think the benefits are modest. I think the thing to remember about many of these elderly men is that they've got lots of other co-morbidities that complicate this issue. And I think when you add some of these other concerns about safety into this, I

think the risk factors accumulate substantially and that's the basis for my voting no.

DR. MORTIMER: Joan Mortimer. I voted no for the reasons that Dr. Richardson said. I think the risks far outweigh the benefit here, even if the risk of cancer recurrence isn't defined for certain.

DR. BUZDAR: Buzdar. I voted no for two reasons. One is that there is evidence that, yes, there was a reduction on the vertebral fracture, but overall fracture reduction was not statistically significant. And also, I think looking at the FDA report, where there's almost 50 percent adverse impact on the disease progression, I think that is an important issue which means that they have not shown clearly that it has a better therapeutic index.

DR. MARGOLIS: David Margolis. I voted yes for my previously stated reasons.

DR. NELSON: Larry Nelson. I voted yes, because I thought this was a well-designed study. It followed 1,500 men for three years and prospectively looked at hard markers. But I have to add I have some concern. I couldn't vote yes for breast cancer as a

gynecologist, because why didn't they have a similar type of design for the breast cancer.

MR. GOOZNER: I voted no because I see some real risks here. And I also see that this is a patient population with cancer, and so it should be treated more like a cancer trial and not like a bone density trial in this case, especially when the company is already out there with this drug, testing it against cancers, because there is some hint it could work that way. It seemed to me that this is the way they should have gone with this trial, rather than simply going for a bone density indication.

The real risk, it seems to me here, is that if they were to get the bone density indication, that this drug will be widely used off label as a cancer therapeutic without evidence of really having benefit of that, and that strikes me as not really where we want to go. That was Merrill Goozner.

DR. JOHNSON: Julia Johnson. I voted yes. I did think that this was a strong study. It clearly did a lot better job at looking at the potential benefit of this medication for these cancer survivors.

And I was impressed by the fact that they were able to show no difference in the bone CTs or the PSA. That really made it much it a much stronger study than the breast cancer study.

DR. CARSON: And I, Carson, yes. And again, the same as Dr. Nelson and Johnson. And I'm so disappointed that I couldn't vote yes because there were no hard markers in the breast cancer study.

DR. BENNETT: Dr. Bennett, and I voted yes for all the reasons that the rest of you have well stated.

DR. UZEL: Gulbu Uzel. I voted yes in agreement with all the reasons mentioned before me.

DR. ROSEN: I voted yes, too, because I thought that it was a well-designed study and there was fracture efficacy. And these relatively low risk older gentlemen have significant morbidity from fracture, and I think we need to have a drug out there that reduces fracture.

DR. COLLINS: Collins. I voted yes, again in agreement with many of the statements said before, but I would like to add that it's a cautious yes with

concern still over safety and again emphasizing the need for the ongoing follow up studies. And again, concern that the 12 time dose metastatic prevention study -- that those data -- it's questionable whether they'll inform this group of patients at all.

DR. CARSON: Okay. The committee voted in favor of a favorable risk benefit ratio demonstrated for denosumab for the treatment of bone loss associated with hormone ablation therapy in men with prostate cancer receiving androgen deprivation therapy. And I think it was the consensus of the committee that there was a demonstrated efficacy in reducing a fracture in these men and as well as the committee felt that the long-term safety risk, or at least the safety risk demonstrated was -- showed with hard markers and that were not surrogate markers.

Let's move on to question 4B. Is a favorable risk benefit ratio demonstrated for denosumab for the prevention of bone loss associated with hormone ablation therapy in men with prostate cancer receiving androgen deprivation therapy? So once again, essentially a similar question to 4A,

except for the prevention rather than the treatment of bone loss. And let's open the discussion of the panel. So the same issues --

Dr. Rosen, go ahead.

DR. JOHNSON: Can I ask a question, though, of the osteoporosis experts? I mean I was amazed that the T-score on average was minus .36. So a pretty normal T-score for these gentlemen, but yet a number of them had fractures.

So is prevention different from this group? Because this was not what looked like a high risk group, but they had a number of fractures. I mean, my tendency is to say prevention is a hard thing to determine in terms of prevention of osteoporotic fractures. This group seems somewhat unique to me however.

DR. ROSEN: So I don't know, was that spine T-score or was it hip? Spine.

DR. JOHNSON: That was lumbar.

DR. ROSEN: Yeah, yeah. So generally those -- spine BMD goes up with age. They had advanced age at 75, so it's not as good a risk

predictor anyways in the age group over 65, but I would argue with a 23 percent prevalent rate; 23 percent of them had vertebral fractures. That's pretty high for an older population of men. And the fact is, having been on hormonal ablation therapy, that puts them at high risk.

So I mean it highlights the issue that I think we got back to with prevention that BMD is not the end all to be all. And in this situation, you need clinical judgment to identify people at risk. And a male that is undergoing hormone ablation therapy is going to lose significant bone over a significant period of time.

DR. JOHNSON: So are you suggesting that men who are getting this treatment, probably do need prevention generally as a group?

DR. ROSEN: Well I think that most people who are on hormonal ablation therapy, most men are getting some form of treatment one way or the other in terms of biphosphonates. I think in most people that are being referred, we see it. They're on a biphosphonate, although the data on that isn't nearly

as strong as it is from this prevention trial.

So, I mean, when a patient comes in, I don't look at the bone density and say you're not at risk because your T-score is zero. I say, you could have been plus two and have lost 20 percent of your bone density over the six years of hormonal ablation therapy.

DR. CARSON: Dr. Collins?

DR. COLLINS: Yes. What I'm struggling with here is so -- I mean if the question is in this group of patients who have been on androgen deprivation for three years to start with and a third of them have osteoporosis because they have vertebral fractures, should that group be treated? Yes.

If I confine my thinking to that, it's clear. But if I have to extend to the guy whose just diagnosed with prostate cancer, and he's getting ready to go on androgen deprivation therapy, should he get a biphosphonate? Should he get this drug? I'm not sure where I stand.

DR. CARSON: Well again, we're asked to look at whether the data we have before us demonstrated

that this drug prevented bone loss.

DR. ROSEN: Can I just make a point -- and then the way the question is phrased, if they had gone back to some of the original questions, which were, is there a subgroup of individuals that are at high risk and had a favorable risk profile for prevention, that would be a little more comforting because Dr. Collins is right. Otherwise, we open it up to say everybody who's started on ablative therapy is going to get treatment or everybody who's got -- initiated ablative therapy. And it's not true that everybody gets therapy immediately with ablation nor that everybody loses bone with ablative therapy. But if we identify those people at higher risk -- so I think the question is a little more global and maybe it should be more specific.

DR. CARSON: Go ahead, Dr. Collins.

DR. COLLINS: And I think Mr. Goozner's point is really well taken. You can see it that a drug gets approved and then it gets given to people who -- to everybody. And I guess that's not really our concern.

DR. CARSON: And I think that's probably why -- point well taken, Dr. Rosen. But I think that's probably why this question is quite global and quite inclusive, because it's closer to how clinically it gets used.

Dr. Mortimer? Oh, it's Dr. Buzdar?

DR. BUZDAR: Yes. I think the thing which we again have to keep in mind, that we are being asked is it a favorable risk benefit ratio, and I think that question has not been answered clearly. Because over here, the control arm is placebo. There are effective therapies. And then you see the slide that placebo if you -- in other words, did nothing, survival was identical. Outcome was identical, these patients who did not get any therapy. So I personally think that if you look at the other side of the coin, that maybe the answer is no.

DR. CARSON: Dr. Margolis?

DR. MARGOLIS: Sure. David Margolis. I think we need to be careful and think about what the study was designed to show and I think it was designed to show treatment, and many of these people were

fairly sick. It wasn't designed to look at somebody who's just initiating care. I also think it's important to realize, unless I'm forgetting the studies, that in every one of these studies, while the word placebo is being used, they were all treated with Vitamin D and calcium, which in some parts of this country and other countries is considered a therapy for osteopenia and osteoporosis.

DR. CARSON: Dr. Nelson?

DR. NELSON: Dr. Rosen, I wonder can you clarify for me. I thought hypogonadism was a major risk factor for osteoporosis. So why wouldn't you want to start somebody -- a male -- that we have this evidence. Why wouldn't you want to start him on this to prevent osteoporosis?

DR. ROSEN: Well, I mean I think there are other options, calcium and Vitamin D. Not everybody who gets hormone ablative therapy -- just like post-menopausal women, some women after chemotherapy don't lose bone. It's not an absolute. And what worries me is that it's clear that treatment of bone loss in question 4A, is the treatment of bone loss -- it's

established they have bone loss. We're treating those.

Here, we're preventing something that we're not sure is going to happen. I mean it's likely to happen, but it requires follow up. So what we do often with our men is say we'll repeat your bone density in two years and we'll see if you've lost bone. And not all of them do. So that's my concern about prevention versus treatment in this population. I don't think you can globally -- everybody's at risk with ablative therapy.

DR. NELSON: Right. Well, the reason I ask is say you have a patient like that and two years later you do their bone density and it's dropped a lot, but it's still not osteoporotic. Wouldn't you start treating then?

DR. ROSEN: Yes, I would. I would. I don't care what their absolute number is. If they've lost significant bone, I would treat them. And that's what question 4A is and that's why I was so insistent. But when we talk about prevention of something that may or may not occur, that's a different story.

DR. NELSON: No, but I'm talking about -- it would still be prevention if they don't have osteoporosis yet, but they're on their way towards it based on your two years of observation. So my view would be, if you do get evidence that they're deteriorating, we should be able to use this as prevention before they get to osteoporosis.

DR. MORTIMER: I'm sort of struck that the way the committee has sort of lined out are the oncologists are the folks that are worried about the increased risk. And I think I speak for my colleagues on either side of me, if there's any suspicion that your cancer is going to come back earlier, that is a risk that outweighs anything, especially since there are other therapies. And I suspect our cancer advocate would say the same. If there's any suspicion that there's an increased risk of cancer recurrence, it is not worth it and that is an incredible risk.

MR. GOOZNER: Dr. Rosen, you made two comments. I'm curious. Earlier you said that there was no treatment and then you said we could give them biphosphonates. So which is it?

DR. ROSEN: -- established, there hasn't been a randomized trial is what I'm saying, of this degree to show that. That's all. That's what I was trying to say. That there's no FDA approved treatment currently for this. There are studies that suggest it, but there isn't a randomized controlled of this degree. That's all I was trying to establish. There clearly are treatments for bone loss in these individuals, and biphosphonates have been the first line therapy.

DR. CARSON: Dr. Kehoe?

DR. KEHOE: Yes. I just wanted to clarify for Dr. Nelson. If you recall the slide that we showed on the indications, for treatment of bone loss in men undergoing hormone ablation therapy, that included patients that were on therapy and had demonstrated significant bone loss. We would place those patients in a treatment category, not in the prevention category.

DR. NELSON: Even if they were not osteoporotic yet.

DR. KEHOE: Yes.

DR. CARSON: Dr. Uzel?

DR. UZEL: I had one comment. In the field of immunology and infectious disease, there are definite guidelines; what you do, what you treat, who you treat. We are discussing about approval of a medication in a field where -- in a subset of patients where there are no good guidelines.

How do you approach the patient, how do you -- what do you call high risk and who do you treat? What's the best effort to treat this patient? So you can see the dilemma between the members of the committee. And I guess I would like you to take consideration when making your decision, voting for this question. Just my comment.

DR. CARSON: Any other comments for the committee before we vote? Summaries? No. Okay. Let's vote.

Is there a favorable risk benefit ratio demonstrated for denosumab for the prevention of bone loss associated with hormone ablation therapy in men with prostate cancer receiving androgen deprivation therapy?

We did so well last time. Let's try again. If all the committee members could vote again. All right. Got it. Three committee members voted yes and eleven, no.

So if we would start with you, Dr. Collins?

DR. COLLINS: Collins. I voted no. I think it falls short when we consider prevention as opposed to treatment in that we aren't really entirely clear of the natural history in this disease and we have remaining questions about safety.

DR. ROSEN: I'm Dr. Cliff Rosen, and Dr. Mortimer scared me. And I think that I would have -- I would actually -- I think that her point, some of her points on the other side of the room from that group, that's always diametrically opposed to us, are correct. And I think when we talk about prevention, it's different than treatment. So the subtlety of the words are important, and I would not like to see a global indication for everybody to go on this until we're sure that the risk benefit is okay.

DR. UZEL: Gulbu Uzel. I voted no. I also gave into the oncologists, which is not usual for the

infectious disease team to give in to oncologists, but I agree that the risk safety concerns are unclear for this population.

DR. BENNETT: John Bennett. I voted yes. I believe we have a population between 14 and 1,500 patients. And we've looked at disease progression with three different parameters. and it does not seem to me like there is a sizable risk.

How do we know what's safe? It takes huge patient populations to know what's absolutely safe. But for the moment, I think this was safe enough for approval.

DR. CARSON: Carson. I voted yes. I was convinced that this does prevent a drop in bone mineral density and those hard endpoints, again, convinced me of the relative safety. And once again, as an obstetrician, gynecologist, I'm so sad to see this study not duplicated in women.

DR. JOHNSON: Julia Johnson. I voted no. I thought in terms of prevention, as with the other uses of this medication, that that's a softer usage. Clearly, the men who were at high risk could use it

for treatment, but I want to wait a bit before we consider it for prevention.

MR. GOOZNER: I voted no. As I said earlier, I think that when you're treating cancer patients that you've got to have higher standards than just simply treating a side effect of the treatment and for a drug that may influence the cancer.

DR. NELSON: Larry Nelson. I voted no, but actually I was going to vote yes, right up until the last minute. And the reason I voted no is because I agree with Dr. Rosen's perspective of, yes, let's get some data that their bone density is declining and then initiate therapy, because as I read the question it talks about bone loss. It's not talking about treatment of osteoporosis or prevention of osteoporosis. It's talking about treatment or prevention of bone loss. So the bone loss can still be prevented under the treatment paradigm. So that's why I voted no for this.

DR. MARGOLIS: David Margolis. I voted no, really for the same reason. I think a fine treatment study was done, but we still need a fine prevention

study.

DR. BUZDAR: Buzdar. I voted no, because of concerns that it has not shown that it is safe to administer the antibody and that it has no adverse effect on the outcome of the disease.

DR. MORTIMER: Mortimer. No.

DR. RICHARDSON: Richardson. No. I think the safety concerns are real with this drug. The other aspect that I wanted to point out is the fact that when it comes to the issue of prevention, when you look at the use of a drug like zoledronic acid over the last several years in the medical oncology field, I think everybody has kind of revisited that particular drug with respect to schedule and how it's used. For some reason this got into the monthly types of regimens.

I think everybody has taken a second look at that and realized if you're really treating osteoporosis in these men, you treat them as though they have osteoporosis. That is once a year. I think there's a lot of stuff that is given out there for prevention, which rather than being preventive

medicine may be remunerative medicine.

DR. GULLEY: Gulley. I voted yes for the same reasons that Dr. Bennett and Dr. Carson already mentioned. Thanks.

MS. SOLONCHE: Solonche. I voted no.

DR. CARSON: Okay. Any other comments from the committee that need to be in the record?

Okay, well the committee voted against there being a favorable risk benefit ratio demonstrated for denosumab for the prevention of bone loss associated with hormonal ablation therapy in men with prostate cancer receiving androgen deprivation therapy. And the consensus of the committee was that there was not evidence as to the drug's safety in patients with prostate cancer and that this possible risk did not justify the issue of not being able to precisely choose in which patients this drug would prevent bone loss.

Okay. Well our session is over and again, this -- oh, I guess not. Sorry, I guess I'm hungry, right? I missed a total page. Okay.

Prior to the approval of an indication for

treatment or prevention of bone loss in patients with cancer, receiving hormone ablation, should data from studies designed to evaluate the effects of denosumab on skeletal related events, bone metastasis, in advanced cancers be required to be submitted to the agency for review to determine if there are any detrimental effects on cancer outcomes. So we just vote.

DR. COLLINS: I don't know that those studies as they've been described to us and the cancer metastasis preventions -- were the doses going to be 12 times the dose that's here? I think if we're worried about long-term bone effects from over suppression with this dose, at a dose 12 times this doses, you know, we're going to see a different set of problems. And I don't know that that study necessarily really informs this dose in this patient population, personally.

DR. CARSON: Other? Yes?

DR. BUZDAR: Yes. I think the question -- if I understand the question correctly, the thing is that in cancer patients giving the

antibody therapy, number one thing which the sponsor has to show is that it is safe. It does not have an adverse outcome on the clinical course of the illness which the patient is being treated. I think that should be a must. And it has to be in very clear way, and stuff has to be there before we go there.

DR. CARSON: Dr. Gulley?

DR. GULLEY: So yeah, I think that the only indication that we have voted for is the prostate cancer indication in which they've showed relatively, I think pretty persuasively, with their bone scan data and their PSA data and their overall survival that there is no difference in this rather large cohort of men. So I think that I would agree with Dr. Collins, that if we're waiting until a study comes in with 12 times the dose, that may inform the -- that may not be the right study to inform the safety for this study.

DR. CARSON: Dr. Mortimer?

DR. MORTIMER: But then maybe I'm misinterpreting the question, but isn't the question just saying what when you're using supportive care therapies, you have to make sure it does not impact on

the underlying malignant disease process, and I mean that's the obvious.

DR. PAZDUR: Correct. Let me give you some clarity here to our general advice --

DR. CARSON: Thank you.

DR. PAZDUR: -- and what we have given to companies. We were not involved with design of these studies, okay, as far as the oncology office was. The issue -- and we have many of these agents, such as radioprotective agents, neuroprotective agents, cardioprotective agents, et cetera, that come to our office. And in general, we ask sponsors to usually have co-primary endpoints of an effect on the endpoint of interest, whether it be, in this case, bone mineralization and then a primary endpoint of a PFS, or survival, et cetera to make sure of that effect.

However, what we're looking at here obviously is a set of studies that have been completed. And what we want to know is, is there any detrimental effect. Again, these are not as good as a prospective evaluation of a time to event endpoint such as survival, progression free survival, but at

least it will give us a hint. In the studies using a higher dose, if we do see an effect, then the question is somewhat answered.

I guess one of the questions that I want to pose, because I think most people would agree to this, is should there be separate studies that look prospectively at this endpoint before these drugs are approved for a cancer agent? So could we change the question? Because would most people probably agree with this? I take from the discussions that people are interested in it.

DR. COLLINS: I agree and, in fact, that was just the point that I was getting at, that the data from the metastasis study is going to be so different from this that it really --

DR. PAZDUR: Okay. So could I change the question to the following?

Should a decision on these products in oncology be deferred until new trials are designed that look at a primary endpoint of survival or progression free survival, some time to event endpoint, in conjunction with a endpoint of bone loss

or fracture prevention, some type of bone endpoint?

DR. CARSON: I think maybe that's why it was a Freudian slip that I missed that last page, but FDA does not like the questions changed. And there has also been a rather standing rule that we don't change the questions.

If I can get some feedback from FDA as to whether or not --

DR. PAZDUR: I am FDA, so --

DR. CARSON: Well I know that, but I just wondered if you were the most senior FDA person, okay?

DR. PAZDUR: Yes, I am the most senior person here, so I can change the question, because I wrote the first question.

DR. CARSON: Okay. So you were the one who wrote it. You were the one who wrote them? Okay. So you're changing it then and to -- go ahead.

DR. PAZDUR: Should there be new trials that are initiated that look at a co-primary endpoint that are cancer related, outcome related, i.e., progression free survival or survival?

DR. CARSON: And are you asking for this

specific drug rather than as a general rule regarding REMs.

DR. PAZDUR: Correct. Right.

DR. CARSON: Okay.

DR. COLLINS: This drug in this dose, correct?

DR. PAZDUR: What's that? Yes.

DR. MARGOLIS: And you want the data from that trial -- you're suggesting the data from that trial be available before --

DR. CARSON: Approval.

DR. PAZDUR: Correct.

MR. GOOZNER: Question.

Dr. Pazdur, isn't there a difference between testing a drug that makes sure that the cancer doesn't get worse, so it's a safety signal?

DR. PAZDUR: It's a safety signal.

MR. GOOZNER: As opposed to an improvement in the cancer which is a cancer drug.

DR. PAZDUR: I think that's a good point too; you know, the issue of a loss of having the drug available to these populations versus having

definitive proof here. And here again, I'm bringing this question up for discussion and a vote.

DR. CARSON: And could you just -- looking a little ahead -- now the new question, how does that differ from 6A?

DR. COLLINS: Well there's a problem here because the committee voted yes to 6A, but no to 6B and this -- or excuse me -- 4A and 4B, but then this question here is treatment or prevention lumped together. So we already said yea for treatment and nay for prevention, when now they're lumped here and so --

DR. CARSON: Well he's saying any approval before the drug is --

DR. COLLINS: We'll be contradicting ourselves to some -- some of us will be contradicting ourselves if we want to vote yes here.

DR. CARSON: No. All he's saying is prior to approval of any indication should -- right? Should there be additional studies to show that the drug doesn't have an effect on cancer?

DR. COLLINS: But if we voted yes to 4A,

then we should vote no to this.

DR. MARGOLIS: Well then what have we been doing for the last 45 minutes?

DR. JOHNSON: It also doesn't address the prostate versus breast cancer. It says all. Okay.

DR. CARSON: Dr. Nelson?

DR. PAZDUR: So you want to change another question.

UNIDENTIFIED SPEAKER: Well I suggest that we delete the question or we all vote abstain.

DR. PAZDUR: Okay. Why don't we go back to the original question then? Okay. Would people feel comfortable with just looking at the data from existing studies and making some conclusions? We'll go back to the original question.

DR. CARSON: I guess that rule stands.

DR. PAZDUR: Okay.

DR. CARSON: Okay. So what the question is, is that prior to the approval of this drug for any approval, either treatment or prevention, should there be additional data or studies that are related specifically to the drug's effects on skeletal related

events in advanced cancer patients.

DR. MARGOLIS: Isn't that what we've been doing for the last 45 minutes and some people who voted no said they wanted more data? Some people voted yes, thought there was enough data. I mean how is that any -- I mean are we going to revisit the last 45 minutes?

DR. CARSON: So the question is, do you want more data?

DR. MARGOLIS: But we already answered that. I mean some people said no, they wanted more data. Some people said yes, they thought the data was sufficient, that the risk profile was such that it should be used for treatment. I mean, that's what we've been talking about for about 45 minutes now.

DR. CARSON: Dr. Buzdar?

DR. BUZDAR: I think the thing-- which if I as an oncologist -- the first thing is in oncology you want to look at it, that what is anything you do has impact on the outcome of the disease, i.e., cancer. So I think that has to be the most important thing. An intervention altering one aspect of the disease,

but overall affecting adversely the disease process for which we are treating, is I think an adverse effect. I think it doesn't make any sense to approve that type of approach.

DR. CARSON: Dr. Nelson?

DR. NELSON: I hope we delete the question.

DR. PAZDUR: If people feel that we've already answered this question, then that's fine with us. Okay.

DR. CARSON: Okay, so --

DR. PAZDUR: We can move on.

DR. CARSON: The summary of the discussion here is that we have, in essence, given our advice to FDA and this question has in essence already been answered.

DR. PAZDUR: Okay.

DR. CARSON: Okay. Ms. Solonche?

MS. SOLONCHE: My reading of this question, it's talking about here the prevention of bone loss, whereas we have been talking in some cases about fracture. I think that's a major difference in this question. I don't see what's wrong with this

question.

DR. CARSON: I think what the question asks is, is there more data needed in both bone loss -- for approval for both bone loss prevention or fracture treatments. And the committee has in essence felt that there, in fact, was enough data present and we have in fact voted on that.

MS. SOLONCHE: Is this perhaps a question that is looking to the future, not at this particular treatment, and maybe that is something we should be concerned about, not at this meeting but at another time and a different place?

DR. PAZDUR: We already have stated policy in guidance that address this issue.

DR. CARSON: Okay. Let's move on to question 6A.

If approved, do you recommend that denosumab have a risk evaluation and mitigation strategy or REMs?

Is the committee familiar with REMs? It was mentioned in the first slides I think today.

Okay, shall we open up this for discussion?

Dr. Collins?

DR. COLLINS: Could someone from the FDA clarify for me exactly what a communication plan to disseminate information to healthcare providers is? What that looks like, how that is? An example perhaps of a drug that it's used for.

DR. BEITZ: Yeah, this is unlike a medication guide, which is information geared to patients in lay language. A communication plan would be something that the sponsor would undertake to disseminate information about the risks of the drug to prescribers and could include mailings of letters. It could include website information. It could include CME courses, that sort of thing.

DR. CARSON: Dr. Bennett?

I'm, sorry. Dr. Bennett?

DR. BENNETT: The company has already presented a post-marketing surveillance plan, and how is this different than we're asking from what the company already proposed that they're going to do?

DR. BEITZ: Okay. The pharmacovigilance plan would be designed to do risk assessment, to

identify signals. This has more to do -- the REMs, at least the medication guide and communication plan, have to do with communicating risk to persons, either patients or prescribers. It doesn't have to do anything with assessing risk.

DR. CARSON: Dr. Uzel?

DR. UZEL: I just wanted to give an example of the guidance that is distributed to the patients. Like when we prescribe quinolones like Levaquin to our patients, levofloxacin, the pharmacy when they're dispensing the medication, gives a little information thing that you are at risk of tendon rupture. So I guess this is an example of what a communication plan is that would be disseminated to the patients, right?

DR. BEITZ: A medication guide would be given to patients, and it's an FDA reviewed paper. It's a piece of paper that lists the risks that are in the package insert that professionals see, but it's written in lay terms. And that's given to the patients at the time that the patients generally either pick up a prescription or are dispensed the medication in the doctor's office. The communication

plan is geared to doctors and healthcare providers.

DR. CARSON: Dr. Nelson?

DR. NELSON: Would it be appropriate to get some information from the sponsor about their opinion about this?

DR. CARSON: No, actually we just want the -- FDA would just like to have the committee's opinion. They will solicit the opinion of the sponsor separately.

Dr. Buzdar?

DR. BUZDAR: Yes, I think the thing is that it is important to -- more education does not hurt anybody. I think if there is more information which is disseminated to the healthcare provider and to the consumer, I think it is always good. I would support that.

DR. CARSON: Okay. Any other comments before we vote?

Okay. So if approved, do you recommend that denosumab have a risk evaluation and mitigation strategy? There are 12 of the committee members who voted yes and one voted no. So let's go around and

see.

MS. SOLONCHE: Martha Solonche. I voted yes.

DR. GULLEY: James Gulley. I voted yes. I think that when there's a potential for a safety signal, I think it's important to have informed consent for the patients and for the physicians treating, and I think this may help.

DR. RICHARDSON: Ron Richardson. I voted yes.

DR. BUZDAR: Buzdar. I voted yes.

DR. MARGOLIS: David Margolis. I voted yes.

DR. NELSON: Larry Nelson. I voted yes. And in fact, we should have a risk reduction and evaluation and mitigation strategy for everybody in this country.

MR. GOOZNER: I voted yes, and I would just add that I think it's especially important to have these kinds of strategies when you have a first in class drug.

DR. JOHNSON: Julia Johnson. I voted yes.

DR. CARSON: I voted no, because I don't

know that there is evidence to say that REMs actually is very helpful and just not costly.

DR. BENNETT: John Bennett. I voted yes, but I am concerned about the drain on healthcare dollars and physicians in healthcare deliverers' time. It's not clear to me whether it's going to be -- this bang is going to be worth the buck.

DR. UZEL: Gulbu Uzel. I voted yes as well, and I agree with Dr. Bennett regarding the concerns about the time and money we will spend on this.

DR. ROSEN: I voted yes. I think it's extremely important to clarify to practitioners what they're dealing with, especially first in class drugs.

DR. COLLINS: Collins. I voted yes for reasons previously stated.

DR. CARSON: The committee voted overwhelming in favor of a REMs strategy, and the consensus is that any educational piece to inform practitioners of the facts about especially this new class of drugs would be beneficial. So let's move to the last question.

If so, which elements should be included in

the REMs? A medication guide to inform patients about the risk of the drugs? A communication plan to disseminate information to healthcare providers? And any other issues. Let me open the discussion.

DR. BUZDAR: Number 3 should have been both.

DR. COLLINS: Yeah, it -- do we have -- can we choose one or the other?

DR. BUZDAR: I think we should change that to both. Third choice should be both.

DR. CARSON: Dr. Margolis?

DR. MARGOLIS: I agree. I think with a first in class drug, we're -- whether people voted yes or no, there's always been concerns about safety, that those safety risks need to be well communicated to both patients and providers.

DR. CARSON: Any other issues?

MR. GOOZNER: Yeah, this is all in the realm of hypothetical but it was triggered by comments from some of the physicians on the panel about the cost of this. I mean I don't know where we're going to be in five years or so, but it strikes me, as a person who works in a different industry and profession, that the

idea that we're going to have a doctor giving a shot in an office and we can't record who got it and what happened to that person, and then get that back to the Food and Drug Administration over time in a reasonable fashion, it strikes me as like $1.38 in today's electronic environment, except if you don't have an electronic environment.

And so I think that we ought to talk about the real costs of having a real risk mitigation strategy. I don't know that this is the right drug to have a registry for, but it certainly seems to be the kind of drug that you could easily have a registry for, because it is going to be administered in a physician's office.

DR. CARSON: Dr. Johnson?

DR. JOHNSON: Yes, I support that concept. I really do think this is so new and unique, and I think a lot of the things we said today reflected our concerns about the use of this medication, even though we do see the value and the studies were well designed, it really is important to get back the information on the potential long-term effects.

DR. CARSON: Other comments? Dr. Nelson?

DR. NELSON: I also like the idea of a registry.

DR. CARSON: Dr. Uzel?

DR. UZEL: I want to comment on if a physician feels, himself or herself, qualified to give this medication in his office. This is for the consumer advocates. The physician, you would assume, would be well communicated and knowledgeable about the risks and benefits of this medication. I just want to highlight the misbelief or distrust in the medical field. So I just want to assure you, and that's why everybody does what they do.

MR. GOOZNER: If I may respond. It's not out of distrust. It's -- one of the things -- I mean I've sat on a number of FDA advisory committees, and one of the things that we see over and over again is a lack of data about outcomes.

When we talk about risk evaluation, mitigation strategies, which were really a fairly new I think to the FDA -- and I think that they are struggling with how to do this. And I think that we

as advisors, that we should articulate that there is a new world coming, hopefully in medicine, in which we can gather a lot more information, a lot more easily about the use of drugs. And that as thought leaders, hopefully, that we should articulate that vision here.

So it's not a question about -- what physicians have done in the past shouldn't be what physicians aren't going to do in the future.

DR. CARSON: Any other questions before we go on to question number 7? Just teasing. That was preventing people from leaving the room.

The committee had suggested in their consensus to go forth and recommend a REM strategy, that perhaps a registry be one of these strategies as well as a patient information guide and a communication plan for disseminating information to healthcare practitioners.

Now the real end of the meeting is -- thank you, again, for all of your participation. I've certainly enjoyed spending this day with all of you and have learned a lot. Hopefully, you all agree with that. Thank you again. Bye.

[Whereupon, at 4:59 p.m., the meeting was adjourned.]